Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

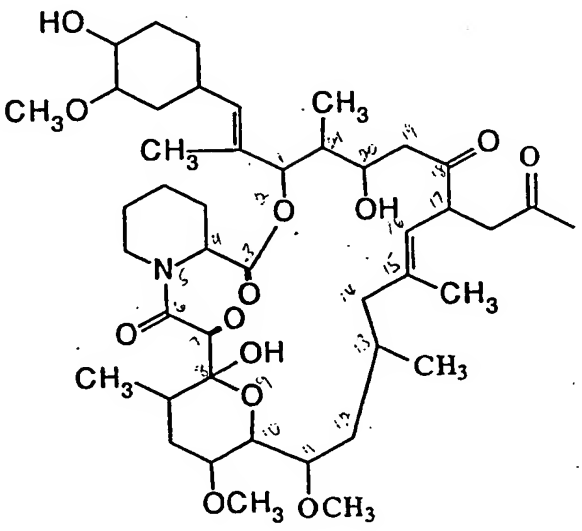
Title of Invention: Macrolide

Inventors (please provide full names): Paul Alexander Jones

Earliest Priority Filing Date: 7/21/99

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please search A method for preventing or treating acute or chronic cerebral neurodegenerative diseases, which comprises administering the compound (I)



(I)

a tacrolimus

Please include inventors search

Thanks

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Searcher: _____

Searcher Phone #: _____

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Date Searcher Picked Up: _____

Date Completed: _____

Searcher Prep & Review Time: _____

Clerical Prep Time: _____

Online Time: _____

PTO 1681 (8-01)

Type of Search

NA Sequence (#)_____

AA Sequence (#)_____

Structure (#) _____

Bibliographic _____

Litigation _____

Fulltext _____

Patent Family _____

Other _____

Vendors and cost where applicable

STN _____

Dialog _____

Questel Orbit: _____

Dr Links _____

Lexis Nexis _____

Sequence Systems _____

WWW Internet _____

Other (specify) _____

=> fil capl; d que l12; fil medl;d que l16; fil wpids;d que l19; dup rem l16,l12,l19
FILE 'CAPLUS' ENTERED AT 15:55:11 ON 15 SEP 2003
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FILE COVERS 1907 - 15 Sep 2003 VOL 139 ISS 12
FILE LAST UPDATED: 14 Sep 2003 (20030914/ED)

inventor search

This file contains CAS Registry Numbers for easy and accurate substance identification.

L10 5075 SEA FILE=CAPLUS ABB=ON JONES P?/AU
L11 12712 SEA FILE=CAPLUS ABB=ON (NEURODEGEN? OR NEUROPROTECT? OR NEURO(A)(DEGEN? OR PROTECT?))/OBI
L12 13 SEA FILE=CAPLUS ABB=ON L10 AND L11

FILE 'MEDLINE' ENTERED AT 15:55:11 ON 15 SEP 2003

FILE LAST UPDATED: 13 SEP 2003 (20030913/UP). FILE COVERS 1958 TO DATE.

On April 13, 2003, MEDLINE was reloaded. See HELP RLOAD for details.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2003 vocabulary. See http://www.nlm.nih.gov/mesh/changes2003.html for a description on changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

L14 3034 SEA FILE=MEDLINE ABB=ON JONES P?/AU
L15 23595 SEA FILE=MEDLINE ABB=ON (NEURODEGEN? OR NEUROPROTECT? OR NEURO(A)(DEGEN? OR PROTECT?))
L16 7 SEA FILE=MEDLINE ABB=ON L14 AND L15

FILE 'WPIDS' ENTERED AT 15:55:11 ON 15 SEP 2003

FILE LAST UPDATED: 10 SEP 2003 <20030910/UP>
MOST RECENT DERWENT UPDATE: 200358 <200358/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> NEW WEEKLY SDI FREQUENCY AVAILABLE --> see NEWS <<<

>>> PATENT IMAGES AVAILABLE FOR PRINT AND DISPLAY <<<

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L17 531 SEA FILE=WPIDS ABB=ON JONES P?/AU
L18 13851 SEA FILE=WPIDS ABB=ON (NEURODEGEN? OR NEUROPROTECT? OR NEURO(A)(DEGEN? OR PROTECT?))
L19 11 SEA FILE=WPIDS ABB=ON L17 AND L18

FILE 'MEDLINE' ENTERED AT 15:55:12 ON 15 SEP 2003

FILE 'CAPLUS' ENTERED AT 15:55:12 ON 15 SEP 2003
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FILE 'WPIDS' ENTERED AT 15:55:12 ON 15 SEP 2003
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PROCESSING COMPLETED FOR L16
PROCESSING COMPLETED FOR L12
PROCESSING COMPLETED FOR L19
L20 25 DUP REM L16 L12 L19 (6 DUPLICATES REMOVED)
ANSWERS '1-7' FROM FILE MEDLINE
ANSWERS '8-16' FROM FILE CAPLUS
ANSWERS '17-25' FROM FILE WPIDS

=> d ibib ab 1-25

L20 ANSWER 1 OF 25 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2001295914 MEDLINE
DOCUMENT NUMBER: 21273541 PubMed ID: 11377571
TITLE: FK 506 protects brain tissue in animal models of stroke.
AUTHOR: McCarter J F; McGregor A L; **Jones P A**; Sharkey J
CORPORATE SOURCE: Fujisawa Institute of Neuroscience, University of Edinburgh, Edinburgh, Scotland, UK.
SOURCE: TRANSPLANTATION PROCEEDINGS, (2001 May) 33 (3) 2390-2.
Journal code: 0243532. ISSN: 0041-1345.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20010917
Last Updated on STN: 20010917
Entered Medline: 20010913

L20 ANSWER 2 OF 25 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 1998351977 MEDLINE
DOCUMENT NUMBER: 98351977 PubMed ID: 9685693
TITLE: Protection against hippocampal kainate excitotoxicity by intracerebral administration of an adenosine A2A receptor antagonist.
AUTHOR: **Jones P A**; Smith R A; Stone T W
CORPORATE SOURCE: Institute of Biomedical and Life Sciences, Laboratory of Human Anatomy, University of Glasgow, Glasgow G12 8QQ, UK.
SOURCE: BRAIN RESEARCH, (1998 Aug 3) 800 (2) 328-35.
Journal code: 0045503. ISSN: 0006-8993.

PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980917
Last Updated on STN: 19980917
Entered Medline: 19980904

AB We have previously shown that the peripheral administration of an A2A receptor agonist 2-p-(2-carboxyethyl)phenethylamino-5'-N-ethylcarboxamidoadenosine hydrochloride (CGS 21680) protected the hippocampus against kainate-induced excitotoxicity. The present study utilises the intrahippocampal route to further investigate CGS 21680-mediated protection as well as examining the role of adenosine and both A1 and A2A receptors in kainate-induced excitotoxicity. Injections were made directly into the hippocampus of anaesthetised male Wistar rats. Following surgery and the administration of 0.25 nmol kainate in 1 microl of solution, the animals were left to recover for seven days before perfusion and brain slicing. Haematoxylin and eosin staining revealed substantial damage to the CA3 region. Co-administration of the A2A receptor agonist CGS 21680 over a range of doses did not protect the region to any degree. Similarly neither the A1 receptor agonist R-phenylisopropyladenosine (R-PIA), nor adenosine itself reduced kainate-induced damage. The intrahippocampal injection of the selective A2A receptor antagonist, 4-(2-[7-amino-2- 2-furyl 1,2, 4 triazolo 2,3-a 1,3,5 triazin-5-yl-amino]ethyl)phenol (ZM241385) however, significantly decreased kainate damage to the CA3 region. These results show that adenosine A2A receptor-induced protection is most likely to be mediated peripherally and is probably not due to activation of A2A receptors within the hippocampus. The lack of protection observed with either R-PIA or adenosine may be due to an inhibitory action of the A2A receptor on the **neuroprotective** A1 receptor. Importantly, this study also questions the role of endogenously released adenosine in protecting the hippocampus from excitotoxic damage.

L20 ANSWER 3 OF 25 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 1998268730 MEDLINE
DOCUMENT NUMBER: 98268730 PubMed ID: 9607714
TITLE: Protection against kainate-induced excitotoxicity by adenosine A2A receptor agonists and antagonists.
AUTHOR: **Jones P A**; Smith R A; Stone T W
CORPORATE SOURCE: Division of Neuroscience and Biomedical Systems, Institute of Biomedical and Life Sciences, University of Glasgow, UK.
SOURCE: NEUROSCIENCE, (1998 Jul) 85 (1) 229-37.
Journal code: 7605074. ISSN: 0306-4522.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 19980811
Last Updated on STN: 19980811
Entered Medline: 19980727

AB The **neuroprotective** role of adenosine receptor agonists in various models of ischaemia and neuronal excitotoxicity has been attributed to adenosine A1 receptor activation. In this study we examine the role of the A2A receptor in the kainate model of excitotoxicity. Kainate (10 mg/kg) was administered systemically 10 min after the intraperitoneal injection of adenosine analogues. The A2A agonist 2-p-(2-carboxyethyl)phenethylamino-5'-N-ethylcarboxamidoadenosine hydrochloride (CGS21680) protected the hippocampus at concentrations of 0.1 and 0.01 mg/kg, but not at 2 microg/kg. The addition of the centrally

acting adenosine A1 receptor antagonist 8-cyclopentyl-1,3-dipropylxanthine partially reduced protection only in the CA3a region, suggesting that only a small proportion of the protection was attributable to the A1 receptor. A less potent A2A agonist, N6-[2-(3,5-dimethyoxyphenyl)-2-(2-methylphenyl)-ethyl]adenosine (1 mg/kg), provided only partial protection against kainate. 4-(2-[7-Amino-2-[2-furyl][1,2,4]triazolo[2,3-a][1,3,5]triazin-5-yl -amino]ethyl)phenol, a selective A2A antagonist, also showed protection against kainate-induced neuronal death, when administered alone or in combination with CGS21680. These results show that adenosine A2A receptor activation is protective against excitotoxicity. The protection is largely independent of A, receptor activation or blockade.

L20 ANSWER 4 OF 25 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 96426300 MEDLINE
DOCUMENT NUMBER: 96426300 PubMed ID: 8828594
TITLE: Prevention by a purine analogue of kainate-induced neuropathology in rat hippocampus.
AUTHOR: MacGregor D G; **Jones P A**; Maxwell W L; Graham D I; Stone T W
CORPORATE SOURCE: Division of Neuroscience and Biomedical Systems, University of Glasgow, UK.
SOURCE: BRAIN RESEARCH, (1996 Jun 24) 725 (1) 115-20.
Journal code: 0045503. ISSN: 0006-8993.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961206

AB Systemic injection of kainic acid produces a characteristic regional and cellular pattern of neuronal loss in the central nervous system by mechanisms which may be relevant to an understanding of **neurodegenerative** disorders. It has previously been found, by measuring the binding of a glial marker ligand, that analogues of adenosine, such as R-N6-phenylisopropyladenosine (R-PIA), can prevent kainate-induced damage of the hippocampus at doses as low as 10 micrograms/kg, i.p. The use of gliotic markers, however, is open to misinterpretation, and the present work was designed to re-examine purine protection against kainate using histological methods. The results show that R-PIA, at a dose of 25 micrograms/kg i.p. in rats, can protect against the neuronal damage caused by kainate and that this protection could be completely prevented by the simultaneous administration of 1,3-dipropyl-8-cyclopentylxanthine, indicating the involvement of adenosine A1 receptors in the protection.

L20 ANSWER 5 OF 25 MEDLINE on STN
ACCESSION NUMBER: 2001441370 MEDLINE
DOCUMENT NUMBER: 21379169 PubMed ID: 11487050
TITLE: Oxidative damage is the earliest event in Alzheimer disease.
AUTHOR: Nunomura A; Perry G; Aliev G; Hirai K; Takeda A; Balraj E K; **Jones P K**; Ghanbari H; Wataya T; Shimohama S; Chiba S; Atwood C S; Petersen R B; Smith M A
CORPORATE SOURCE: Institute of Pathology, Case Western Reserve University, Cleveland, Ohio 44106, USA.
CONTRACT NUMBER: AG09287 (NIA)
AG14249 (NIA)
SOURCE: JOURNAL OF NEUROPATHOLOGY AND EXPERIMENTAL NEUROLOGY, (2001 Aug) 60 (8) 759-67.
Journal code: 2985192R. ISSN: 0022-3069.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010820
Entered Medline: 20010816

AB Recently, we demonstrated a significant increase of an oxidized nucleoside derived from RNA, 8-hydroxyguanosine (8OHG), and an oxidized amino acid, nitrotyrosine in vulnerable neurons of patients with Alzheimer disease (AD). To determine whether oxidative damage is an early- or end-stage event in the process of **neurodegeneration** in AD, we investigated the relationship between neuronal 8OHG and nitrotyrosine and histological and clinical variables, i.e. amyloid-beta (A beta) plaques and neurofibrillary tangles (NFT), as well as duration of dementia and apolipoprotein E (ApoE) genotype. Our findings show that oxidative damage is quantitatively greatest early in the disease and reduces with disease progression. Surprisingly, we found that increases in A beta deposition are associated with decreased oxidative damage. These relationships are more significant in ApoE epsilon4 carriers. Moreover, neurons with NFT show a 40%-56% decrease in relative 8OHG levels compared with neurons free of NFT. Our observations indicate that increased oxidative damage is an early event in AD that decreases with disease progression and lesion formation. These findings suggest that AD is associated with compensatory changes that reduce damage from reactive oxygen.

L20 ANSWER 6 OF 25 MEDLINE on STN
ACCESSION NUMBER: 97062527 MEDLINE
DOCUMENT NUMBER: 97062527 PubMed ID: 8906266
TITLE: Basic mechanisms of kynurenine actions in the central nervous system.
AUTHOR: Stone T W; MacGregor D G; Smith R A; **Jones P**; Behan W M; Graham D I
CORPORATE SOURCE: Institute of Biomedical and Life Sciences, University of Glasgow, Scotland.
SOURCE: ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, (1996) 398 195-201. Ref: 37
Journal code: 0121103. ISSN: 0065-2598.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 19970313
Last Updated on STN: 19970313
Entered Medline: 19970306

L20 ANSWER 7 OF 25 MEDLINE on STN
ACCESSION NUMBER: 96440080 MEDLINE
DOCUMENT NUMBER: 96440080 PubMed ID: 8842391
TITLE: Ascorbate attenuates the systemic kainate-induced neurotoxicity in the rat hippocampus.
AUTHOR: MacGregor D G; Higgins M J; **Jones P A**; Maxwell W L; Watson M W; Graham D I; Stone T W
CORPORATE SOURCE: University of Glasgow, UK.
SOURCE: BRAIN RESEARCH, (1996 Jul 15) 727 (1-2) 133-44.
Journal code: 0045503. ISSN: 0006-8993.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961223

AB The neuronal damage induced by systemic administration of kainic acid reproduces the cellular and regional pattern of damage produced by repeated seizures. The ability of kainic acid to induce lipid peroxidation, and the ability of free radical inhibitors to prevent ischaemically-induced cell death, has led us to examine the possible role of free radicals in kainate-induced injury. Ascorbic acid was able to reduce kainate-induced damage of the rat hippocampus, measured by means of the gliotic marker ligand [3H]PK11195. Ascorbate was significantly effective at doses of 30 mg kg-1 and above, with total protection against kainate at 50 mg kg-1. Histologically, ascorbate at 50 mg kg-1 was able to prevent kainate-induced neuronal loss in the hippocampal CA1 and CA3a cell layers. The antioxidant was also effective when administered simultaneously with, or 1 h before the kainate. Protection was also obtained by allopurinol, 175 mg kg-1 and by oxypurinol, 40 mg kg-1. Ascorbate did not modify synaptically evoked potentials or long-term potentiation in hippocampal slices, ruling out any blocking activity at glutamate receptors. It is concluded that the neuronal damage produced by systemically administered kainate involves the formation of free radicals.

L20 ANSWER 8 OF 25 CAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2002:408674 CAPLUS
DOCUMENT NUMBER: 137:6187
TITLE: Preparation of 1,2,4-triazolo[3,4-a]phthalazines as selective partial or full inverse agonists for the GABAA receptor .alpha.5 subunit in the treatment of **neurodegenerative** diseases or cognitive deficits
INVENTOR(S): Chambers, Mark Stuart; **Jones, Philip**; MacLeod, Angus Murray; Maxey, Robert James; Szekeres, Helen Jane
PATENT ASSIGNEE(S): Merck Sharp & Dohme Limited, UK
SOURCE: PCT Int. Appl., 95 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002042305	A1	20020530	WO 2001-GB5164	20011122
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002023084	A5	20020603	AU 2002-23084	20011122

PRIORITY APPLN. INFO.: GB 2000-28583 A 20001123
WO 2001-GB5164 W 20011122
OTHER SOURCE(S): MARPAT 137:6187

AB Title compds. [I; A = (un)substituted alkylidene, bond; L = O, S, NH, alkylamino, cycloalkylamino; X = (un)substituted 5-membered heterocyclodiyl with 1-4 N, O, or S atoms of which .ltoreq.1 atom is either O or S, (un)substituted 6-membered heterocyclodiyl with 1-3 N atoms (un)fused to a benzene or heteroaliph. ring; Y = alkylidene optionally

substituted with an oxo group, (CH2)nO; n = 2-4; Z = (un)substituted 5-membered heterocyclodiyl with 1-3 N, O, or S atoms in which if one atom is either O or S, .gtoreq.1 N atom is present, (un)substituted 6-membered heterocyclodiyl with 2-3 N atoms; R1 = H, halo, NC, F3C, F3CO, alkyl, alkenyl, alkynyl, alkoxy, alkenyloxy, alkynyloxy substituted with 1-2 halo or with (un)substituted pyridyl, Ph; R2 = R1 = H, halo, cyano, F3C, F3CO, alkyl, alkenyl, alkynyl, alkoxy, alkenyloxy, alkynyloxy substituted with 1-2 halo; if A = alkylidene, R20, R21 = H, alkyl, cycloalkyl, cycloalkenyl, alkenyl, alkynyl, aminoalkyl, phenylalkyl, or R20R21 = heterocyclyl, heteroaryl; if A = bond, R20R21 = (un)substituted heterocyclic ring] such as II are prepd. E.g., addn. of N2H4.H2O to 1,4-dichlorophthalazine, coupling with 5-methyl-3-isoxazolecarboxylic acid and heating with Et3N.HCl in PhMe gives III. Monolithiation of 2,5-dibromopyridine and addn. to DMF, redn. of the aldehyde with NaBH4, silylation of the free alc., lithiation of the remaining bromine and addn. to DMF, and redn. of the aldehyde moiety gives 5-(tert-butyldimethylsiloxymethyl)-2-pyridinemethanol (IV). Coupling of III and (IV) with (Me3Si)2NLi, desilylation with TBAF, mesylation of the free alc., and displacement of the mesylate with Me2NH gives II. I all possess Ki values of <100 nM for displacement of [3H]Ro 15-1788 from the .alpha.5-subunit of the GABAA receptor; some possess Ki values <1 nM.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 9 OF 25 CAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 2

ACCESSION NUMBER: 2001:63812 CAPLUS
DOCUMENT NUMBER: 134:110473
TITLE: New use of a macrolide tacrolimus analog as a **neuroprotectant** agent
INVENTOR(S): **Jones, Paul Alexander**; Sharkey, John; Kelly, John Shearer
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 9 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001005385	A2	20010125	WO 2000-GB2788	20000719
WO 2001005385	A3	20010802		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1196170	A2	20020417	EP 2000-946165	20000719
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2003504396	T2	20030204	JP 2001-510442	20000719

PRIORITY APPLN. INFO.: GB 1999-17158 A 19990721
WO 2000-GB2788 W 20000719

AB A macrolide tacrolimus analog I is provided for use as a neuroprotective agent, particularly for preventing or treating acute or chronic cerebral neurodegenerative diseases.

L20 ANSWER 10 OF 25 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2002:976917 CAPLUS
DOCUMENT NUMBER: 139:127169
TITLE: The role of immunophilins in focal cerebral ischemia: evidence of **neuroprotection** by FK506
AUTHOR(S): McGregor, A. L.; **Jones, P. A.**; McCarter, J. F.; Allsopp, T. E.; Sharkey, J.
CORPORATE SOURCE: Fujisawa Inst. of Neurosci., Edinburgh, UK
SOURCE: Immunosuppressant Analogs in Neuroprotection (2003), 231-261. Editor(s): Borlongan, Cesario V.; Isacson, Ole; Sanberg, Paul R. Humana Press Inc.: Totowa, N. J.
CODEN: 69DJYZ; ISBN: 0-89603-944-7
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English

AB A review. The development of therapies designed to ameliorate CNS tissue damage assocd. with stroke, traumatic brain injury, and spinal cord injury has been described as a chronicle of failed projects and unmet expectations. More than 100 agents have been examd. in clin. trials, but few have shown convincing clin. benefit. Consequently, there is essentially no effective treatment targeting acute or chronic neurodegeneration in the nervous system. A measured degree of success has been achieved with tissue plasminogen activator (tPA). However, since administration must be within 3 h of stroke onset, thrombolysis is only beneficial in around 5 % of stroke patients. The macrolide immunosuppressant FK506 (tacrolimus) was originally developed to prevent allograft rejection, but has been shown to display a striking potential to prevent neurodegeneration following both ischemia and chemotoxicity, and to improve the regeneration of axotomized nerve fibers in animal models. FK506 is one of the few agents to consistently protect in a variety of stroke models, including transient and permanent models of focal ischemia and in both forebrain and global ischemia and in a variety of species. The precise mechanism underlying the neuroprotective action of FK506 has yet to be elucidated. This review examines the potential mechanisms of FK506 neuroprotection with respect to the immunophilins. Although the precise mechanism underlying the neuroprotective action of FK506 is not known, the formation of mol. complexes with immunophilins allows interaction at a no. of fundamental steps in the ischemic cascade. All neuroprotective agents examd. to date have targeted a specific pathway of the ischemic cascade, for example, NMDA-receptor antagonists or Ca2+ channel blockers. While these compds. reduced infarct vol. in preclin. investigations, it is not surprising that agents that target a single stage in such a complex chain of events do not produce a large clin. impact. The application of FK506 and its non-immunosuppressive derivs. is therefore a promising strategy for the treatment of neurodegeneration.

REFERENCE COUNT: 234 THERE ARE 234 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 11 OF 25 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:318977 CAPLUS
DOCUMENT NUMBER: 135:90953
TITLE: Mitochondrial abnormalities in Alzheimer's disease
AUTHOR(S): Hirai, Keisuke; Aliev, Gjumrakch; Nunomura, Akihiko; Fujioka, Hisashi; Russell, Robert L.; Atwood, Craig S.; Johnson, Anne B.; Kress, Yvonne; Vinters, Harry V.; Tabaton, Massimo; Shimohama, Shun; Cash, Adam D.; Siedlak, Sandra L.; Harris, Peggy L. R.; **Jones, Paul K.**; Petersen, Robert B.; Perry, George; Smith, Mark A.
CORPORATE SOURCE: Institute of Pathology, Case Western Reserve University, Cleveland, OH, 44106, USA
SOURCE: Journal of Neuroscience (2001), 21(9), 3017-3023
CODEN: JNRSDS; ISSN: 0270-6474

Searched by Barb O'Bryen, STIC 308-4291

PUBLISHER: Society for Neuroscience
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The finding that oxidative damage, including that to nucleic acids, in Alzheimer's disease is primarily limited to the cytoplasm of susceptible neuronal populations suggests that mitochondrial abnormalities might be part of the spectrum of chronic oxidative stress of Alzheimer's disease. In this study, we used in situ hybridization to mitochondrial DNA (mtDNA), immunocytochem. of cytochrome oxidase, and morphometry of electron micrographs of biopsy specimens to det. whether there are mitochondrial abnormalities in Alzheimer's disease and their relationship to oxidative damage marked by 8-hydroxyguanosine and nitrotyrosine. We found that the same neurons showing increased oxidative damage in Alzheimer's disease have a striking and significant increase in mtDNA and cytochrome oxidase. Surprisingly, much of the mtDNA and cytochrome oxidase is found in the neuronal cytoplasm and in the case of mtDNA, the vacuoles assocd. with lipofuscin. Morphometric anal. showed that mitochondria are significantly reduced in Alzheimer's disease. The relationship shown here between the site and extent of mitochondrial abnormalities and oxidative damage suggests an intimate and early assocn. between these features in Alzheimer's disease.
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 12 OF 25 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:799629 CAPLUS
DOCUMENT NUMBER: 136:307350
TITLE: The role of kynurenines in the production of neuronal death, and the **neuroprotective** effect of purines
AUTHOR(S): Stone, T. W.; Behan, W. M. H.; **Jones, P. A.**; Darlington, L. G.; Smith, R. A.
CORPORATE SOURCE: Institute of Biomedical & Life Sciences, University of Glasgow, Glasgow, G12 8QQ, UK
SOURCE: Journal of Alzheimer's Disease (2001), 3(4), 355-366
CODEN: JADIF9; ISSN: 1387-2877
PUBLISHER: IOS Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The kynurenine metabolic pathway from tryptophan accounts for a large proportion of the metab. of this amino acid in the brain. Although a major route for the generation of the essential co-factor NAD (NAD), two components of the pathway have marked effects on neurons. Quinolinic acid is an agonist at N-methyl-D-aspartate (NMDA)-sensitive glutamate receptors, while kynurenic acid is an antagonist and, thus, a potential neuroprotectant. The levels of quinolinic acid are known to increase substantially following cerebral insults or infection, and has been most clearly implicated in the AIDS-dementia complex. The actions of quinolinic acid and NMDA show subtle differences, however, which suggest other factors contributing to cell damage. In this article we review the evidence that free radicals may be involved in the neurotoxic effects of quinolinic acid and consider the possibility that quinolinic acid might be involved in Alzheimer's disease. Finally, adenosine receptor ligands can modulate neuronal damage, supporting the view that they may represent suitable targets for the development of novel neuroprotectant drugs for the treatment of Alzheimer's and other neurodegenerative disorders.
REFERENCE COUNT: 127 THERE ARE 127 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 13 OF 25 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:342051 CAPLUS
DOCUMENT NUMBER: 135:131617

TITLE: **Neuroprotection** by A2A receptor antagonists
AUTHOR(S): Stone, Trevor W.; **Jones, Paul A.**; Smith, Robert A.
CORPORATE SOURCE: Division of Neuroscience and Biomedical Systems, University of Glasgow, Glasgow, G12 8QQ, UK
SOURCE: Drug Development Research (2001), 52(1/2), 323-330
CODEN: DDREDK; ISSN: 0272-4391
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 71 refs. Activation of AA receptors has been shown to protect neurons in the hippocampus from damage caused by excitotoxins or from cerebral insults such as ischemia. For example, the A2A agonist 2-p-(2-carboxyethyl)phenethylamino-5'-N-ethylcarboxamidoadenosine hydrochloride (CGS 21680) protects the hippocampus at concns. which are only partially blocked by the centrally acting adenosine A1 receptor antagonist 8-cyclopentyl-1,3-dipropylxanthine (CPX), suggesting that protection is mediated largely by the A2A receptor. However, selective antagonists at the A2A receptor, such as 4-(2-[7-amino-2-{2-furyl}{1,2,4}triazolo{2,3-a}{1,3,5}triazin-5-yl-amino]ethyl)phenol (ZM 241385), also show protection against neuronal death produced by ischemia or excitotoxicity. In addn., A2A receptor antagonists can reduce damage produced by combinations of subthreshold doses of the endogenous excitotoxin quinolinic acid and free radicals. The TdT-mediated dUTP-biotin nick end labeling (TUNEL) method has revealed that, after systemic kainic acid administration, staining was apparent in the CA1 region of the hippocampus only, even though damage was present in both the CA1 and CA3a areas. In animals injected intrahippocampally, both apoptosis and damage were limited to the CA3 region. Intrahippocampal co-injection of kainate together with ZM 241385 did not induce apoptosis even though damage was apparent. This suggests that the adenosine A2A receptor may play a role in the route by which cells die during excitotoxicity. Overall, A2A receptor antagonists appear to be promising candidates as new drugs for the prevention of neuronal damage and death in the central nervous system.
REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 14 OF 25 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:45912 CAPLUS
DOCUMENT NUMBER: 137:149526
TITLE: Evidence of in vivo **neuroprotection** by FK506 and cyclosporin A
AUTHOR(S): Sharkey, J.; **Jones, P. A.**; McCarter, J. F.; Carlson, G. J.; Sato, N.
CORPORATE SOURCE: Fujisawa Institute of Neuroscience, University of Edinburgh, Edinburgh, UK
SOURCE: Immunophilins in the Brain: FKBP Ligands: Novel Strategies for the Treatment of Neurodegenerative Disorders, [Proceedings from the Conference on Neuroimmunophilins], 1st, Schlangenbad, Germany, July 9-11, 1999 (2000), Meeting Date 1999, 147-164. Editor(s): Gold, Bruce G.; Fischer, Gunter; Herdegen, Thomas. Prous Science: Barcelona, Spain.
CODEN: 69CEO5; ISBN: 84-8124-165-2
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review on the antiischemic actions of FK506 and cyclosporin A. Preclin. studies have shown that FK506 and CsA are potent antiischemic agents in a variety of tissues and species. In the brain, neuroprotection can be elicited by a single immunosuppressant dose of FK506 72 h before and up to 2 h after the insult. CsA is similarly neuroprotective, although its poor blood-brain barrier permeability necessitates the use of high doses,

making it unsuitable for use in stroke patients. Studies on FK506, CsA, SDZ ASM 981 (FK506 analog), and rapamycin point to the involvement of calcineurin in the pathophysiol. of stroke.
REFERENCE COUNT: 161 THERE ARE 161 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 15 OF 25 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:92736 CAPLUS
DOCUMENT NUMBER: 133:48
TITLE: Calcineurin inhibitors as **neuroprotectants**: focus of tacrolimus and cyclosporin
AUTHOR(S): Sharkey, John; **Jones, Paul A.**; McCarter, Jennifer F.; Kelly, John S.
CORPORATE SOURCE: University Department of Neuroscience, Fujisawa Institute of Neuroscience, Edinburgh, UK
SOURCE: CNS Drugs (2000), 13(1), 1-13
CODEN: CNDREF; ISSN: 1172-7047
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 207 refs. Tacrolimus (FK506) and cyclosporin (cyclosporin-A) are potent immunosuppressants which are presently in clin. use for the treatment of allograft rejection. Recent studies suggest that tacrolimus and cyclosporin may also be of therapeutic benefit for the treatment of neurodegenerative disorders, in particular those assocd. with acute brain ischemia. At immunosuppressive doses, tacrolimus is a powerful neuroprotectant in many exptl. models of cerebral ischemia: reducing infarct vol. and improving neurol. outcome. In rat focal ischemia models neuroprotection can be elicited by a single injection of tacrolimus given up to 72 h before or up to 2 h after the insult. A similar postocclusion window of efficacy has been reported in the gerbil forebrain ischemia model. These neuroprotective properties are also shared by cyclosporin, although the poor penetration of cyclosporin across the blood-brain barrier necessitates the use of high doses (20 mg/kg) of this drug to achieve neuroprotection. The observation that sirolimus (rapamycin) is not neuroprotective in models of focal cerebral ischemia, but can effectively inhibit the neuroprotective effects of tacrolimus, supports the view that the protective effects of tacrolimus are mediated via the inhibition of calcineurin.
REFERENCE COUNT: 207 THERE ARE 207 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 16 OF 25 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:367819 CAPLUS
DOCUMENT NUMBER: 129:104071
TITLE: Protection by an adenosine analog against kainate-induced extrahippocampal neuropathology
AUTHOR(S): Macgregor, D. G.; Graham, D. I.; **Jones, P. A.**; Stone, T. W.
CORPORATE SOURCE: Division of Neuroscience and Biomedical Systems, University of Glasgow, Glasgow, G12 8QQ, UK
SOURCE: General Pharmacology (1998), 31(2), 233-238
CODEN: GEPHDP; ISSN: 0306-3623
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The glutamate analog kainic acid produces neuronal damage in the central nervous system. We have reported that analogs of adenosine, such as R-N6-phenylisopropyladenosine (R-PIA) can, at doses as low as 10 .mu.g/kg IP, prevent the hippocampal damage that follows the systemic administration of kainate. The present work was designed to examine

purine protection against kainate in extrahippocampal regions by using histol. methods. The results show that R-PIA, at a dose of 25 .mu.g/kg IP in rats, can protect against the neuronal damage caused by kainate in the basolateral amygdaloid nuclei, the pyriform cortex and around the rhinal fissure. This protection could be prevented by the simultaneous administration of the A1 adenosine receptor antagonist 1,3-dipropyl-8-cyclopentylxanthine, confirming that the protection involved adenosine A1 receptors. No protection was obsd. in the posterior amygdaloid nuclei or the entorhinal cortex, suggesting the absence of relevant adenosine receptors or a different mechanism of excitotoxicity.

REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 17 OF 25 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
ACCESSION NUMBER: 2003-586823 [55] WPIDS
DOC. NO. CPI: C2003-158648
TITLE: Composition useful for enhancing cognition comprises imidazopyridines, pyrimidines or triazine compounds.
DERWENT CLASS: B02
INVENTOR(S): BETTATI, M; CHAMBERS, M S; HUMPHRIES, A C; **JONES**, **P**; LEWIS, R T; MAXEY, R J; SZEKERES, H J; TEALL, M R
PATENT ASSIGNEE(S): (MERI) MERCK SHARP & DOHME LTD
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003048132	A1	20030612	(200355)*	EN	63

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003048132	A1	WO 2002-GB5337	20021127

PRIORITY APPLN. INFO: GB 2001-28499 20011128
AB WO2003048132 A UPAB: 20030828
NOVELTY - A composition comprises imidazopyridines, pyrimidines or triazine compounds and a carrier.
DETAILED DESCRIPTION - A composition comprises imidazopyridines, pyrimidines or triazine compounds of formula (I) and a carrier.
X, Y = CH or N;
R1 = H, hydrocarbon, heterocyclic group, halo, cyano, trifluoromethyl, nitro, -ORa, -SRa, -SORa, -SO2Ra, -SO2NRaRb, -NRaRb, -NRaCORb, NRaCO2Rb, -CORa, -CO2Ra, -CONRaRb or -CRa=NORb;
Ra, Rb = H, hydrocarbon or heterocyclic group;
V', W' = H, halo, 1-6C alkyl, OH or 1-6C alkoxy;
Z' = H, halo, CN, NO2, CF3, OCF3, CF2H, SCF3, R2, OR3, SR3, (CH2)pN(R3)2, O(CH2)pN(R3)2, SO2R2, SO2N(R3)2, COR4, CO2R3, CON(R3)2, NHCOR4, NR10(CH2)n-heteroaryl, or O(CH2)n-heteroaryl (where the heteroaryl is optionally mono- - tri-substituted by 1-6C alkyl, benzyl, (CH2)pN(R3)2, halo or CF3);
R10 = 1-6C alkyl;
n = 1 - 2;
p = 0 - 2;

R2 = 1-6C alkyl, 3-6C cycloalkyl, 3-6C cycloalkyl-1-4C alkyl, 2-6C alkenyl, 2-6C alkynyl or heteroaryl (all optionally substituted by halo, CN, NO2, CF3, OCF3, CF2H, SCF3, OH, 1-4C alkoxy, 1-4C alkoxycarbonyl, amino, 1-4C alkylamino or di(1-4C alkyl)amino);
R3 = H or R2;
NR3+R3 = 5 - 7 membered non-aromatic heterocyclic ring; and
R4 = R3 or heteroaryl.
Provided that:
(1) when X is CH, then Y is CH; and
(2) at least one of V', W' and Z' is other than H.
ACTIVITY - Nootropic; **Neuroprotective**.
MECHANISM OF ACTION - GABA-A receptor inhibitor.
Inhibitor of the binding of (3H)-flumazenil to the benzodiazepine binding site of human gamma -aminobutyric acid-A (GABA-A) receptor containing the alpha 5 subunit stably expressed in Ltk cells. (I) was tested for its activity as an inhibitor of the binding of (3H)-flumazenil to the benzodiazepine binding site of human gamma -aminobutyric acid-A receptor and was found to possess a Ki value for displacement of (3H)Ro 15-1788 from the alpha 5 subunit of the human GABA-A receptor of at most 1 nM. No results for specific compounds are given.
USE - (I) is used for the manufacture of a medicament for enhancing diminished cognition and for treating Alzheimer's disease; and for use in therapy (claimed). Also useful for treating cognition deficits due to traumatic injury, stroke, Parkinson's disease, Down's syndrome, age related memory deficits and attention deficit disorder. For a condition associated with GABA-A receptors comprising the alpha 5 subunit.
ADVANTAGE - The compounds have a good binding affinity for the alpha 5 subunit of the GABA-A receptor relative to alpha 1 - alpha 3 subunits.
Dwg.0/0

L20 ANSWER 18 OF 25 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
ACCESSION NUMBER: 2003-103266 [09] WPIDS
DOC. NO. CPI: C2003-025981
TITLE: New human regulator of G-protein signaling protein 9 polypeptide fragment and evectin polypeptide, useful for treating neurological disorders e.g., Alzheimer's disease or Parkinson's.
DERWENT CLASS: B04 D16
INVENTOR(S): **JONES, P G**; YOUNG, K H
PATENT ASSIGNEE(S): (AMHP) WYETH
COUNTRY COUNT: 100
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002079401	A2	20021010	(200309)*	EN	132

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW
US 2003166850 A1 20030904 (200359)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002079401	A2	WO 2002-US9064	20020322
US 2003166850	A1 Provisional	US 2001-279240P	20010328
		US 2002-108210	20020327

PRIORITY APPLN. INFO: US 2001-279240P 20010328; US 2002-108210 20020327

AB WO 200279401 A UPAB: 20030206

NOVELTY - Isolated human regulator of G-protein signaling protein 9 (RGS9) polypeptide fragment and evectin polypeptide are new.

DETAILED DESCRIPTION - New isolated human regulator of G-protein signaling protein 9 (RGS9) polypeptide fragment and evectin polypeptide .The human regulator of G-protein signaling protein 9 (RGS9) polypeptide fragment comprises an evectin polypeptide binding domain and the amino acid 461-602 of the 671 amino acid sequence. The human evectin polypeptide fragment comprises a RGS9 polypeptide binding domain and the amino acid 79-136 of the 189 amino acid sequence.

INDEPENDENT CLAIMS are also included for the following:

(1) an isolated polynucleotide comprising 2016 base pairs (bp) sequence and encoding the RGS9 polypeptide fragment, or comprising 570 bp sequence and encoding the evectin polypeptide fragment;

(2) an isolated polypeptide dimer comprising the RGS9 and evectin polypeptides;

(3) an antibody specific for the RGS9-evectin dimer, or the RGS9 or evectin polypeptide fragment;

(4) a transgenic animal;

(5) a recombinant expression vector comprising the polynucleotide;

(6) a genetically engineered host cell, transfected, transformed or infected with the vector;

(7) assaying (M1) the effects of test compounds on the activity of a RGS9-evectin polypeptide dimer, on the transgenic animal or on the binding interaction of RGS9 and evectin polypeptides;

(8) producing (M2) the transgenic animal;

(9) modulating (M3) G-protein activity in a subject;

(10) diagnosis (M4) of a disease or susceptibility to a disease in subject related to the activity of RGS9-evectin dimer; and

(11) treating (M5) a subject in need of enhanced RGS9-evectin dimer activity.

ACTIVITY - **Neuroprotective**; Antiparkinsonian.

No biological data given.

MECHANISM OF ACTION - RGS9-Antagonist; RGS9-Agonist; Evectin-Antagonist; Evectin-Agonist.

No biological data given.

USE - The methods are useful for assaying the effects of test compounds on the activity of a RGS9-evectin polypeptide dimer and transgenic animal, producing a transgenic animal, modulating G-protein activity in a subject and diagnosis of a disease or susceptibility to a disease in a subject related to the activity of a RGS9-evectin dimer. The methods are also useful for the treatment of a subject in need of enhanced RGS9-evectin dimer activity, or inhibiting RGS9-evectin dimer activity (claimed).The polypeptide is useful for treating neurological disorders e.g., Alzheimer's disease or Parkinson's.

Dwg.0/1

L20 ANSWER 19 OF 25 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN

ACCESSION NUMBER: 2003-103216 [09] WPIDS

DOC. NO. CPI: C2003-025944

TITLE: New imidazo-pyrimidine derivatives as gamma amino butyric acid-A receptor ligands, useful in the treatment of e.g. anxiety, agoraphobia and convulsions.

DERWENT CLASS: B02

INVENTOR(S): BLACKABY, W P; CASTRO PINEIRO, J L; CHAMBERS, M S; GOODACRE, S C; HALLETT, D J; **JONES**, P; LEWIS, R T; MACLEOD, A M; MAXEY, R J; MOORE, K W; STREET, L J

PATENT ASSIGNEE(S): (MERI) MERCK SHARP & DOHME LTD

COUNTRY COUNT: 99

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002076983 A1		20021003	(200309)*	EN	127

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002076983 A1		WO 2002-GB1354	20020319

PRIORITY APPLN. INFO: GB 2001-28157 20011123; GB 2001-7358 20010323

AB WO 200276983 A UPAB: 20030206

NOVELTY - Imidazo-pyrimidine derivatives or their salts are new.

DETAILED DESCRIPTION - Imidazo-pyrimidine derivatives of formula (I) or their salts or prodrugs are new;

Z1 = furan, thiophene, pyrrole, (is)oxazole, (iso)thiazole, imidazole, pyrazole, oxadiazole, thiadiazole, triazole, tetrazole, pyridine, pyrazine, pyrimidine or pyridazine (all optionally substituted);

R1 = H, hydrocarbon, heterocyclic group, halogen, cyano, trifluoromethyl, nitro, -ORa, -SRa, -SORa, -SO2Ra, -SO2NRaRb, -NRaRb, -NRaCORb, -NRaCO2Rb, -CORa, -CO2Ra, -CONRaRb or -CRa=NORb;

Ra and Rb = H, hydrocarbon or heterocyclic group.

INDEPENDENT CLAIMS are also included for:

(1) the preparation of (I); and

(2) the use of (I) in the manufacture of medicament for the treatment and/or prevention of adverse neurological conditions.

ACTIVITY - Tranquilizer; Analgesic; Antiemetic; Relaxant; Auditory; Uropathic; Nootropic; **Neuroprotective**; Antimigraine; Neuroleptic; Vasotropic; Antidepressant; Antialcoholic.

MECHANISM OF ACTION - GABAA receptor ligand agonists and inverse agonists.

Compounds of formula (I) displaced the binding of (3H)-flumazenil to the benzodiazepine binding site of human gamma amino butyric acid (GABAA) receptor, with a Ki value of 100nM or less.

Test details are described, but no results for specific compounds are given.

USE - For the preparation of medicament for the treatment and/or prevention of adverse neurological conditions (claimed) e.g. anxiety. In the treatment and/or prevention of a variety of disorder of the central nervous system including anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, animal and other phobias including social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic and acute stress disorder, and generalized or substance-induced anxiety disorder; neuroses; convulsions; migraine, depressive or bipolar disorders, e.g. single-episode or recurrent major depressive disorder, dysthymic disorder, bipolar I and bipolar II manic disorders, and cyclothymic disorder; psychotic disorders including schizophrenia; **neurodegeneration** arising form cerebral ischemia, attention deficit hyperactivity disorder, speech disorders, including stuttering, and disorders of circadian rhythm, e.g. subjects suffering from the effects of jet lag or shift work. For the treatment of pain and nociception; emesis, including acute, delayed and anticipatory emesis, in particular emesis induced by chemotherapy or radiation as well as motion sickness, and post-operative nausea and vomiting, eating disorders including anorexia nervosa and bulimia nervosa, premenstrual

syndrome, muscle spasm or spasticity, hearing disorders, including tinnitus and age-related hearing impairment, urinary incontinence and the effects of substance abuse or dependency, including alcohol withdrawal. Also useful for enhancing cognition, Alzheimer's disease and as radioligands in assays for detecting compounds capable of binding to the human GABAA receptor.

ADVANTAGE - The compounds show good affinity as ligand for the alpha 2, alpha 3 and/or alpha 5 subunit of human GABAA receptor, and are potent inhibitors of the binding of 3H-flumazenil to the benzodiazepine binding site of human GABAA receptors containing the alpha 2, alpha 3 and/or alpha 5 subunit stably expressed in Ltk cells.

Dwg.0/0

L20 ANSWER 20 OF 25 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
ACCESSION NUMBER: 2003-018789 [01] WPIDS
CROSS REFERENCE: 2003-092832 [08]
DOC. NO. CPI: C2003-004569
TITLE: New imidazo-pyrimidine derivatives as Gamma-aminobutyric acid (GABA) receptor agonists, useful for treating e.g. anxiety, neuroses, convulsions, migraine, depressive or bipolar disorders.
DERWENT CLASS: B02
INVENTOR(S): CHAMBERS, M S; GOODACRE, S C; HALLETT, D J; JENNINGS, A; **JONES, P**; LEWIS, R T; MOORE, K W; RUSSELL, M G N; STREET, L J; SZEKERES, H J
PATENT ASSIGNEE(S): (CHAM-I) CHAMBERS M S; (GOOD-I) GOODACRE S C; (HALL-I) HALLETT D J; (JENN-I) JENNINGS A; (JONE-I) JONES P; (LEWI-I) LEWIS R T; (MOOR-I) MOORE K W; (RUSS-I) RUSSELL M G N; (STRE-I) STREET L J; (SZEK-I) SZEKERES H J; (MERI) MERCK SHARP & DOHME LTD
COUNTRY COUNT: 99
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002074773	A1	20020926	(200301)*	EN	197
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW					
US 2002193385	A1	20021219	(200303)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002074773	A1	WO 2002-GB1352	20020319
US 2002193385	A1 Div ex	US 2000-719712	20001215
		US 2002-100797	20020319

FILING DETAILS:

PATENT NO	KIND	PATENT NO
US 2002193385	A1 Div ex	US 6297376

PRIORITY APPLN. INFO: GB 2001-27938 20011121; GB 2001-7134 20010321

AB WO 200274773 A UPAB: 20030204

NOVELTY - Imidazo-pyrimidine derivatives (I), their salts or prodrugs are new.

DETAILED DESCRIPTION - Imidazo-pyrimidine derivatives of formula (I), their salts or prodrugs are new;

X1 = halo, CF3, 1-6C alkyl or 1-6C alkoxy;

X2 = H or halo;

Y = bond, O or NH-linkage;

Z = optionally substituted (hetero)aryl;

R1 = -ORa, -SRa, -S(O)Ra, -SO2Ra, -SO2NRaRb, -NRaRb, -NRaCORb, -NRaCO2Rb, -CORa, -CO2Ra, -CONRaRb, -CRa=NORb, NO2, CF3, CN, halo, heterocyclic group, hydrocarbon or H;

R2 = H or halogen; and

Ra and Rb = H, hydrocarbon or heterocyclic group.

INDEPENDENT CLAIMS are also included for:

(i) the use of (I) in the preparation of a medicament for the treatment and/or prevention of adverse neurological conditions; and

(ii) the preparation of (I).

ACTIVITY - Tranquilizer; Anticonvulsant; Antimigraine; Antidepressant; Neuroleptic; Vasotropic; Analgesic; Antiemetic; Auditory; Nootropic; **Neuroprotective**; Antiparkinsonian; Cerebroprotective; Antiaddictive; Relaxant; Uropathic; Antimigraine.

MECHANISM OF ACTION - Gamma-aminobutyric acid (GABA) receptor agonist.

Test details are described and showed Ki value of at most 100 nM for (I) but no specific results for specific compounds are given.

USE - For the treatment and/or prevention of disorders of the central nervous system such as anxiety (claimed), neuroses, convulsions, migraine, depressive or bipolar disorders, cyclothymic disorder, psychotic disorder (e.g. schizophrenia), speech disorder, pain, post operative nausea and vomiting, hearing impairment, Alzheimer's disease, Parkinson's disease, stroke and Down's syndrome, premenstrual syndrome, muscle spasm, or spasticity, urinary incontinence or substance abuse.

ADVANTAGE - (I) have good affinity as ligands for the alpha -2, alpha -3 and/or alpha -5 subunit of the human GABAA receptor.

Dwg.0/0

L20 ANSWER 21 OF 25 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN

ACCESSION NUMBER: 2003-092832 [08] WPIDS

CROSS REFERENCE: 2003-018789 [01]

DOC. NO. CPI: C2003-023099

TITLE: New imidazo-pyrimidine derivatives useful in the treatment of e.g. anxiety, stress disorders, neuroses, convulsions, migraine, and depressive or bipolar disorders, are gamma amino butyric acid receptor agonists.

DERWENT CLASS: B02

INVENTOR(S): CHAMBERS, M S; GOODACRE, S C; HALLETT, D J; JENNINGS, A; **JONES, P**; LEWIS, R T; MOORE, K W; STREET, L J; SZEKERES, H J

PATENT ASSIGNEE(S): (MERI) MERCK SHARP & DOHME LTD

COUNTRY COUNT: 98

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002074772	A1	20020926	(200308)*	EN	108

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002074772 A1		WO 2002-GB1351	20020319

PRIORITY APPLN. INFO: GB 2001-27938 20011121; GB 2001-7134 20010321

AB WO 200274772 A UPAB: 20030204

NOVELTY - Imidazo-pyrimidine derivatives and their salts are new.

DETAILED DESCRIPTION - Imidazo-pyrimidine derivatives of formula (I) and their salts are new.

X11 = fluoro;

X12 = H or fluoro;

Z = (hetero)aryl optionally substituted by at least one halogen or cyano;

R11 = H, 1-6C alkyl, halo(1-6C)alkyl, dihalo(1-6C)alkyl, hydroxy(1-6C)alkyl, dihydroxy(1-6C)alkyl, (1-6C)alkoxy(1-6C)alkyl, di(1-6C)alkoxy(1-6C)alkyl, cyano(1-6C)alkyl, (2-6C)alkoxycarbonyl(1-6C)alkyl, halogen, cyano, trifluoromethyl, formyl, (2-6C)alkylcarbonyl, (2-6C)alkoxycarbonyl or CR5=NOR6;

R5 = H or 1-6C alkyl; and

R6 = H, 1-6C alkyl, hydroxy(1-6C)alkyl or di(1-6C)alkylamino(1-6C)alkyl.

INDEPENDENT CLAIMS are included for the following:

(1) Preparation of (I); and

(2) Use of (I) in the manufacture of medicament for the treatment and/or prevention of adverse neurological conditions.

ACTIVITY - Tranquilizer; Nootropic; **Neuroprotective**; Antimanic; Antidepressant; Analgesic; Anticonvulsant; Uropathic; Neuroleptic; Antiemetic.

MECHANISM OF ACTION - Gamma amino butyric acid (GABA (A)) receptor agonists. Test details are described, but no results for specific compounds are given.

USE - For the preparation of medicament for the treatment and/or prevention of adverse neurological conditions e.g. anxiety disorders such as panic disorder, agoraphobia, animal and other phobias including social, obsessive-compulsive disorder, stress disorders including post-traumatic and acute stress disorder, generalized or substance-induced anxiety disorder, neuroses, convulsions, migraine, depressive or bipolar disorders, and cyclothymic disorder, psychotic disorders including schizophrenia, **neurodegeneration** arising from cerebral ischemia, dementias, attention deficit hyperactivity disorder, speech disorders including stuttering, and sleep disorders. The may also be useful in the treatment of pain and nociception, vomiting, eating disorders including anorexia and bulimia nervosa, premenstrual syndrome, muscle spasm, or spasticity e.g. paraplegic patients, hearing disorders including tinnitus and age related hearing impairment, urinary incontinence and the effects of substance abuse. They may also be used as an effective pre-medication prior to anaesthesia or minor procedures such as endoscopy, including gastric endoscopy.

ADVANTAGE - The compound show good affinity as ligand for the alpha 2, alpha 3 and/or alpha 5 subunit of human GABA(A) receptor, and are potent inhibitors of the binding of 3H-flumazenil to the benzodiazepine binding site of human GABA(A) receptors containing the alpha 2, alpha 3 and/or alpha 5 subunit stably expressed in Ltk cells.

Dwg.0/0

L20 ANSWER 22 OF 25 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
ACCESSION NUMBER: 2002-049442 [06] WPIDS
DOC. NO. CPI: C2002-013959
TITLE: New histamine receptor, termed H4 useful for detecting H4 (ant)agonists for treating transplanted organ rejection, asthma, allergy, multiple sclerosis and rheumatoid

arthritis.
DERWENT CLASS: B04 D16
INVENTOR(S): BLATCHER, M; **JONES, P G**; PAUSCH, M H; WU, S
PATENT ASSIGNEE(S): (AMHP) AMERICAN HOME PROD CORP
COUNTRY COUNT: 95
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001085786	A2	20011115	(200206)*	EN	66
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001059513	A	20011120	(200219)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001085786	A2	WO 2001-US14527	20010504
AU 2001059513	A	AU 2001-59513	20010504

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001059513	A Based on	WO 2001085786

PRIORITY APPLN. INFO: US 2000-247855P 20001113; US 2000-202151P 20000505; US 2000-227567P 20000823

AB WO 200185786 A UPAB: 20020128
NOVELTY - An isolated histamine receptor, H4 (I), having an amino acid sequence at least 51% identical or comprising at least 10 contiguous amino acids of a fully defined sequence of 390 amino acids (S2) as given in specification, where (I) binds ligands comprising imidazole attached to amine by an alkyl chain, is new.

DETAILED DESCRIPTION - An isolated histamine receptor, H4 (I), having an amino acid sequence at least 51% identical or comprising at least 10 contiguous amino acids of a fully defined sequence of 390 amino acids (S2) as given in specification, where (I) binds ligands comprising imidazole attached to amine by an alkyl chain and the rank order of efficacy of modulation of second messenger formation of the ligands at the H4 receptor protein is 5 greater than 6 equal to 10 greater than 8 equal to 4, where the number represents the number of carbons in the alkyl chain, is new.

INDEPENDENT CLAIMS are also included for the following:

(1) an isolated nucleic acid (II) encoding (I);

(2) an isolated nucleic acid molecule encoding H4 receptor protein, which hybridizes under stringent conditions to a nucleic acid having a sequence of at least 20 nucleotides identical to a corresponding nucleotide sequence of the same number of bases in a fully defined sequence of 1173 nucleotides (S1) as given in the specification or its complement;

(3) a vector (III) comprising (II) operably associated with an expression control sequence;

(4) a host cell (IV) transfected with (III);

(5) a non-human animal (V) transformed with (III), where the animal expresses H4 receptor protein at a detectable level and the cells expressing the H4 receptor protein suppresses cyclic adenosine monophosphate (cAMP) formation when contacted with the H4 receptor agonist;

(6) preparation of (I);

(7) an isolated nucleic acid (VI) of at least 10 bases having a nucleotide sequence identical to a corresponding nucleotide sequence of the same number of bases in (S1) or its complement;

(8) an antibody (VII) which specifically binds to (I);

(9) an assay system (VIII) comprising (IV) to detect an alteration in second messenger accumulation;

(10) an isolated nucleic acid that specifically hybridizes under highly stringent conditions to the complement of (S1), where the nucleic acid encodes histamine H4 receptor protein;

(11) detecting an H4 receptor protein comprising detecting the binding of (VII) to a protein in a sample suspected of containing a H4 receptor protein;

(12) detecting (M1) expression of H4 receptor comprising detecting mRNA encoding H4 receptor in a sample from a cell suspected of expressing H4 receptor;

(13) identifying a test compound that antagonizes or agonizes H4 receptors comprising detecting an increase or decrease respectively in the level of a second messenger in (VIII) contacted with the test compound, where an increase or decrease in the level of the second messenger indicates that the test compound antagonizes or agonizes the H4 receptor; and

(14) identifying (M2) a compound that binds an H4 receptor comprising detecting binding of a test compound to (I).

ACTIVITY - Antirheumatic; antiarthritic; immunosuppressive; antiasthmatic; antiallergic; **neuroprotective**; antidiabetic; cerebroprotective. No supporting data is given.

MECHANISM OF ACTION - cAMP modulator; H4 receptor agonist or antagonist; gene therapy.

USE - (I) is useful for identifying a compound that binds an H4 receptor and detecting expression of H4 receptor.(VII) is useful for detecting an H4 receptor protein which involves detecting binding of (VI) to a protein in a sample suspected of containing H4 receptor protein after contacting the antibody with the sample under conditions that permits specific binding with any H4 receptor protein present in the sample. (VIII) is useful for identifying human H4 receptor (present in an lipid bilayer membrane) ligands and for identifying a test compound that antagonizes or agonizes histamine H4 receptor (all claimed). Modulation of histamine H4 receptors is useful for treating transplanted organ rejection, asthma, allergies and autoimmnue pathologies such as multiple sclerosis, type I diabetes, rheumatoid arthritis, cognitive and memory defects. (I) and (II) are useful targets to identify drugs that are effective in treating disorders associated with histamine-regulated processes. Identification and isolation of (I) provides for development of screening of molecules that interact with H4 receptors. Genetic variants of H4 can be used to diagnose an H4 associated disease as described above. (II) comprising a sequence encoding (I) is useful to treat or prevent a disorder associated with the function of H4 in peripheral blood leukocytes.

Dwg.0/5

L20 ANSWER 23 OF 25 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
ACCESSION NUMBER: 2001-465049 [50] WPIDS
DOC. NO. CPI: C2001-140396
TITLE: New 1,2,3-triazolo(1,5-a)quinazoline compounds active as GABAA receptor inverse agonists, useful for enhancing cognitive function, for treating e.g. Alzheimer's disease, stroke, Parkinson's disease or attention deficit disorder.
DERWENT CLASS: B02
INVENTOR(S): BRYANT, H J; CHAMBERS, M S; **JONES, P**; MACLEOD, A M; MAXEY, R J
PATENT ASSIGNEE(S): (MERI) MERCK SHARP & DOHME LTD; (BRYA-I) BRYANT H J;

(CHAM-I) CHAMBERS M S; (JONE-I) JONES P; (MACL-I) MACLEOD A M; (MAXE-I) MAXEY R J

COUNTRY COUNT: 95

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001044250	A1	20010621	(200150)*	EN	65
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001021954	A	20010625	(200162)		
EP 1242423	A1	20020925	(200271)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
JP 2003516994	W	20030520	(200334)		73
US 2003125333	A1	20030703	(200345)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001044250	A1	WO 2000-GB4752	20001211
AU 2001021954	A	AU 2001-21954	20001211
EP 1242423	A1	EP 2000-985541	20001211
		WO 2000-GB4752	20001211
JP 2003516994	W	WO 2000-GB4752	20001211
		JP 2001-544740	20001211
US 2003125333	A1	WO 2000-GB4752	20001211
		US 2002-149852	20020614

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001021954	A	Based on	WO 2001044250
EP 1242423	A1	Based on	WO 2001044250
JP 2003516994	W	Based on	WO 2001044250

PRIORITY APPLN. INFO: GB 1999-29569 19991214

AB WO 200144250 A UPAB: 20010905

NOVELTY - New 1,2,3-triazolo(1,5-a)quinazoline compounds active as GABAA receptor inverse agonists for enhancing cognitive function are disclosed.

DETAILED DESCRIPTION - 1,2,3-Triazolo(1,5-a)quinazoline compounds of formula (I) and their salts are new:

R1 = H, halogen or CN or 1-4C alkyl, 2-4C alkenyl, 2-4C alkynyl, 1-4C alkoxy, 2-4C alkenyloxy or 2-4C alkynyloxy, each of which is unsubstituted or substituted with 1 or 2 halogen atoms or with a pyridyl or phenyl ring, each of which rings may be unsubstituted or substituted by 1 or 2 halogen atoms or nitro, cyano, amino, methyl or CF3 groups;

R2 = H, halogen or CN or 1-4C alkyl, 2-4C alkenyl, 2-4C alkynyl, 1-4C alkoxy, 2-4C alkenyloxy or 2-4C alkynyloxy, each of which is unsubstituted or substituted with 1 or 2 halogen atoms;

W = a cyclic amine or heteroaromatic group which is optionally joined by a linking group, or other groups such as alkyl or alkoxy; and

Z = a 5- or 6-membered heteroaromatic ring.

Full details are given in the DEFINITIONS (Full Definitions) section.

ACTIVITY - Nootropic; **Neuroprotective**; Cerebroprotective; Vulnerary; Antiparkinsonian; Tranquilizer.

MECHANISM OF ACTION - Gamma aminobutyric acid (GABAA) receptor

inverse agonists.

USE - (I) can be used for enhancing cognition (claimed). They can also be used for the treatment of a subject suffering from reduced cognition e.g. in Alzheimer's disease (claimed). They can also be used for treating cognition deficits due to traumatic injury,, stroke, Parkinson's disease, Downs syndrome, age related memory deficits, attention deficit disorder. The compounds were shown to enhance cognition in the rat water maze test (see WO-A-9625948).

ADVANTAGE - (I) have cognition enhancing effects and can be used with less risk of proconvulsant effects previously described with benzodiazepine receptor partial or full inverse agonists.

Dwg.0/0

L20 ANSWER 24 OF 25 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
ACCESSION NUMBER: 2001-482986 [52] WPIDS
DOC. NO. CPI: C2001-144716
TITLE: New triazolo-pyrimidine compounds active as GABAA receptor ligands, useful for treating e.g. anxiety, neuroses, convulsions, migraine, depression, psychotic disorders, **neurodegeneration**, pain, emesis or eating disorders.
DERWENT CLASS: B02
INVENTOR(S): CHAMBERS, M S; COLLINS, I J; GOODACRE, S C; HALLETT, D J; **JONES, P**; KEOWN, L E; MAXEY, R J; STREET, L J
PATENT ASSIGNEE(S): (MERI) MERCK SHARP & DOHME LTD; (CHAM-I) CHAMBERS M S; (COLL-I) COLLINS I J; (GOOD-I) GOODACRE S C; (HALL-I) HALLETT D J; (JONE-I) JONES P; (KEOW-I) KEOWN L E; (MAXE-I) MAXEY R J; (STRE-I) STREET L J
COUNTRY COUNT: 95
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001044249	A1	20010621	(200152)*	EN	68
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001017200	A	20010625	(200162)		
EP 1244671	A1	20021002	(200265)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
US 2003045532	A1	20030306	(200320)		
JP 2003516993	W	20030520	(200334)		82

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001044249	A1	WO 2000-GB4654	20001205
AU 2001017200	A	AU 2001-17200	20001205
EP 1244671	A1	EP 2000-979818	20001205
		WO 2000-GB4654	20001205
US 2003045532	A1	WO 2000-GB4654	20001205
		US 2002-149851	20020614
JP 2003516993	W	WO 2000-GB4654	20001205
		JP 2001-544739	20001205

FILING DETAILS:

PATENT NO	KIND	PATENT NO

AU 2001017200 A Based on WO 2001044249
EP 1244671 A1 Based on WO 2001044249
JP 2003516993 W Based on WO 2001044249

PRIORITY APPLN. INFO: GB 1999-29687 19991215
AB WO 200144249 A UPAB: 20010914
NOVELTY - Triazolo-pyrimidine compounds (I), are new.
DETAILED DESCRIPTION - Triazolo-pyrimidine derivatives of formula (I) and their salts and prodrugs are new.
Y = H or 1-6C alkyl;
Z' = 1-6C alkyl, 3-7C cycloalkyl, 4-7C cycloalkenyl, 6-8C bicycloalkyl, aryl, 3-7C heterocycloalkyl, heteroaryl, 2-7C alkoxycarbonyl or di(1-6C)alkylamino, all optionally substituted; or
Y+ Z' taken together with the 2 intervening C atoms = a ring selected from 5-9C cycloalkenyl, 6-10C bicycloalkenyl, tetrahydropyridinyl, pyridinyl or phenyl, all optionally benzo-fused and/or substituted;
R1 = 3-7C cycloalkyl, phenyl, furyl, thienyl or pyridinyl, all optionally substituted;
R2 = H, 1-6C alkyl, hydroxy(1-6C)alkyl or 1-6C alkoxy(1-6C)alkyl;
R3 = 1-6C alkyl, 3-7C cycloalkyl(1-6C)alkyl, aryl(1-6C)alkyl, 3-7C heterocycloalkyl or heteroaryl(1-6C)alkyl, any of which may be optionally substituted; or
NR2R3 = a group of formula (i)-(x);
X = O, S, NR5 or CR6R7;
R4 = H, 1-6C alkyl, aryl, 2-7C alkoxycarbonyl or aryl(1-6C)alkoxy(1-6C) alkyl;
R5 = H, 1-6C alkyl, di(1-6C)alkylamino(1-6C)alkyl, 2-6C alkenyl, 3-7C cycloalkyl(1-6C)alkyl, aryl, 3-7C heterocycloalkyl(1-6C)alkyl, heteroaryl, 2-7C alkylcarbonyl or 2-7C alkoxycarbonyl;
R6 = H, halo, OH, 1-6C alkyl, di(1-6C)alkylamino, 2-7C alkoxycarbonyl, or an optionally substituted or phenyl ring-fused 3-7C heterocycloalkyl; and
R7 = H, 1-6C alkyl or an optionally substituted aryl or aryl(1-6C)alkyl.
ACTIVITY - Tranquilizer; Anxiolytic; Anticonvulsant; Analgesic; Antimigraine; Antidepressant; Antimanic; Neuroleptic; **Neuroprotective**; Cerebroprotective; Vasotropic; Nootropic; Antiemetic; Anorectic; Gynecological; Relaxant.
MECHANISM OF ACTION - (I) are ligands for the gamma -amino butyric acid (GABA A receptor alpha 2 and alpha 3 subunits and act as agonists.
The compounds potently inhibit the binding of (3H)-flumazenil to the benzodiazepine binding site of human GABAA receptors containing the alpha 2 or alpha 3 subunits stably expressed in Ltk- cells. The compounds were tested and all found to possess a Ki value for displacement of (3H)-flumazenil from the alpha 2 and/or alpha 3 subunit of the human GABAA receptor of 100 nM or less.
USE - (I) can be used for the treatment and/or prevention of anxiety (claimed). (I) can be used for treating panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, animal and other phobias including post-traumatic and acute stress disorder, and generalized or substance-induced anxiety disorder, neuroses, convulsions, migraine, depressive disorder, dysthymic disorder, bipolar I and bipolar II manic disorders, and cyclothymic disorder, psychotic disorders including schizophrenia, **neurodegeneration** arising from cerebral ischemia, attention deficit hyperactivity disorder, and disorders of circadian rhythm, e.g. in subjects suffering from the effects of jet lag or shift work. They may also be of benefit for pain and nociception, emesis, including acute, delayed and anticipatory emesis, in particular emesis induced by chemotherapy or radiation, as well as post-operative nausea and vomiting, premenstrual syndrome, muscle spasm or spasticity e.g. in paraplegic patients, and hearing loss. They may also be effective

as pre-medication prior to anesthesia or minor procedures such as endoscopy, including gastric endoscopy. The compounds exhibit anxiolytic activity, as may be demonstrated by a positive response in the elevated plus maze and conditioned suppression of drinking tests Psychopharmacol., 1995, 121, 109-117 .

ADVANTAGE - (I) are selective for the alpha 2 and alpha 3 subunits compared to the alpha 1 subunit and have reduced tendency to cause sedation.

Dwg.0/0

L20 ANSWER 25 OF 25 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
ACCESSION NUMBER: 2001-408196 [43] WPIDS
DOC. NO. CPI: C2001-123569
TITLE: New pyrazolo(1,5-d)(1,2,4)-triazine derivatives, are ligands for gamma aminobutyric acid receptors useful for enhancing cognition e.g. in Alzheimer's disease.
DERWENT CLASS: B02
INVENTOR(S): BRYANT, H J; CARLING, W R; CHAMBERS, M S; HOBBS, S C; JONES, P; MACLEOD, A M
PATENT ASSIGNEE(S): (MERI) MERCK SHARP & DOHME LTD
COUNTRY COUNT: 95
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001038331	A2	20010531	(200143)*	EN	54
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001015330	A	20010604	(200153)		
US 6355638	B1	20020312	(200221)		
BR 2000015126	A	20020702	(200252)		
NO 2002002456	A	20020524	(200256)		
CZ 2002001813	A3	20020814	(200263)		
EP 1235829	A2	20020904	(200266)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
SK 2002000895	A3	20021008	(200276)		
KR 2002053091	A	20020704	(200302)		
CN 1391574	A	20030115	(200330)		
HU 2002003579	A2	20030328	(200333)		
JP 2003514909	W	20030422	(200336)		63

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001038331	A2	WO 2000-GB4450	20001122
AU 2001015330	A	AU 2001-15330	20001122
US 6355638	B1	US 2000-717423	20001121
BR 2000015126	A	BR 2000-15126	20001122
		WO 2000-GB4450	20001122
NO 2002002456	A	WO 2000-GB4450	20001122
		NO 2002-2456	20020524
CZ 2002001813	A3	WO 2000-GB4450	20001122
		CZ 2002-1813	20001122
EP 1235829	A2	EP 2000-977692	20001122
		WO 2000-GB4450	20001122
SK 2002000895	A3	WO 2000-GB4450	20001122
		SK 2002-895	20001122

KR 2002053091 A	KR 2002-706672	20020524
CN 1391574 A	CN 2000-816013	20001122
HU 2002003579 A2	WO 2000-GB4450	20001122
	HU 2002-3579	20001122
JP 2003514909 W	WO 2000-GB4450	20001122
	JP 2001-540094	20001122

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001015330	A	Based on	WO 2001038331
BR 2000015126	A	Based on	WO 2001038331
CZ 2002001813	A3	Based on	WO 2001038331
EP 1235829	A2	Based on	WO 2001038331
SK 2002000895	A3	Based on	WO 2001038331
HU 2002003579	A2	Based on	WO 2001038331
JP 2003514909	W	Based on	WO 2001038331

PRIORITY APPLN. INFO: GB 2000-18651 20000728; GB 1999-27874 19991125; GB 2000-9602 20000418

AB WO 200138331 A UPAB: 20010801

NOVELTY - Pyrazolo(1,5-d)(1,2,4)-triazine derivatives (I) are new.

DETAILED DESCRIPTION - Pyrazolo(1,5-d)(1,2,4)-triazine derivatives of formula (I) and their salts are new.

R1 = halo; or 1-6C alkyl, 3-7C cycloalkyl, 4-7C cycloalkenyl, 6-8C bicycloalkyl, 6-10C aryl, 3-7C heterocycloalkyl, heteroaryl or di(1-6C)alkylamino (all optionally substituted by at least one Q);

heteroaryl = 6 membered aromatic ring containing 1-3 N atoms, or 5 membered aromatic ring containing 1-3 O, N or S, but not more than 1 O or S;

Q = halo, R3, OR3, OC(O)R3, NR4R5, NR4R5(1-6C)alkyl, NR4R5C(O), NR4R5C(O)(1-6C)alkyl, CN, cyano(1-6C)alkyl or R6;

R3 = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C cycloalkyl, 3-6C cycloalkyl(1-6C)alkyl, cyano(1 6C)alkyl or hydroxy(1-6C)alkyl (all optionally substituted by 1-3F);

R4, R5 = H, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C cycloalkyl or CF3, or

NR4R5 = 4-7 membered heteroaliphatic ring optionally containing a further N, O or S hetero atom and optionally substituted by at least one R3;

R6 = 6-10C aryl, 6-10C aryl(1-6C)alkyl, heteroaryl or heteroaryl(1-6C)alkyl (all optionally substituted by 1-3 halo or 1-4C alkyl, 2-4C alkenyl, 2-4C alkynyl, 1-4C alkoxy, 2-4C alkenyloxy or 2-4C alkynyloxy (all optionally substituted by 1-3 halo));

L = O, S or NRn;

Rn = H, 1-6C alkyl or 3-6C cycloalkyl;

W = 1-6C alkyl, 2-6C alkenyl or 2 6C alkynyl (all optionally substituted by at least 1 Q'), H, halo, NH2, NO2, CN, OH or halo;

Q' = halo, NH2, NO2, CN, OH or halo;

X = NR4R5, or 5-membered heterocyclic ring containing 1-4 O, N or S heteroatoms, with no more than 1 O or S, or 6 membered heterocyclic ring containing 1-3 N, both optionally fused to benzene or pyridine and optionally substituted by Rx and/or Ry and/or Rz, provided that when X is a pyridine derivative, the pyridine ring is optionally in the form of the N-oxide, and when X is a tetrazole derivative, it is protected by a 1-4C alkyl; or X is phenyl optionally substituted by 1-3 halo, CN, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl or 3-6C cycloalkyl;

Rx = halo, R3, OR3, OC(O)R3, C(O)OR3, NR4R5, NR4C(O)R5, OH, tri(1 6C)alkylsilyl(1-6C)alkoxy(1-4C)alkyl, CN or R6;

Ry = halo, R3, OR3, OC(O)R3, NR4R5, NR4C(O)R5, NR4R5(1-6C)alkyl or CN;

Rz = R3, OR3 or OC(O)R3;

Y = 1-4C alkylene (optionally substituted by oxo) or -(CH2)jO- (where O is nearest X);
j = 2-4, and
Z = 5-membered heteroaromatic ring containing 1-3 O, N or S heteroatoms, with no more than 1 O or S atom, provided that when 1 of the atoms is O or S, then at least 1 N is also present, or 6-membered heteroaromatic ring containing 2 or 3 N with the exception of pyrazine, (both optionally substituted by at least 1 halo, R3, OR3, OC(O)R3, NR4R5, NR4R5(1-6C)alkyl, NR4R5C(O), NR4R5C(O)(1-6C)alkyl, CN, cyano(1-6C)alkyl or R6).

INDEPENDENT CLAIMS are included for the preparation of (I).

ACTIVITY - Nootropic; **neuroprotective**; cerebroprotective; antiparkinsonian.

MECHANISM OF ACTION - Gamma aminobutyric acid (GABA) receptor ligand; alpha 5 subunit partial or full inverse agonist; alpha 1, alpha 2 and alpha 3 subunits antagonists.

In a test to determine inhibition of binding of (3H)-flumazenil to the benzodiazepine binding site of human GABAA receptors containing alpha 5 subunit expressed in Ltk- cells, (I) exhibited Ki values of upto 100 nM.

USE - Used for enhancing cognition, particularly in Alzheimer's disease (claimed), and for treating cognition deficits due to traumatic injury, stroke, Parkinson's disease, Down's syndrome, age related memory deficits and attention deficit disorder.

Dwg.0/0

```
=> fil reg; d stat que l9; fil capl uspatf toxcenter; s l9
FILE 'REGISTRY' ENTERED AT 15:56:27 ON 15 SEP 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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STRUCTURE FILE UPDATES:   14 SEP 2003  HIGHEST RN 585509-69-9
DICTIONARY FILE UPDATES:  14 SEP 2003  HIGHEST RN 585509-69-9

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2003

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

L7                STR
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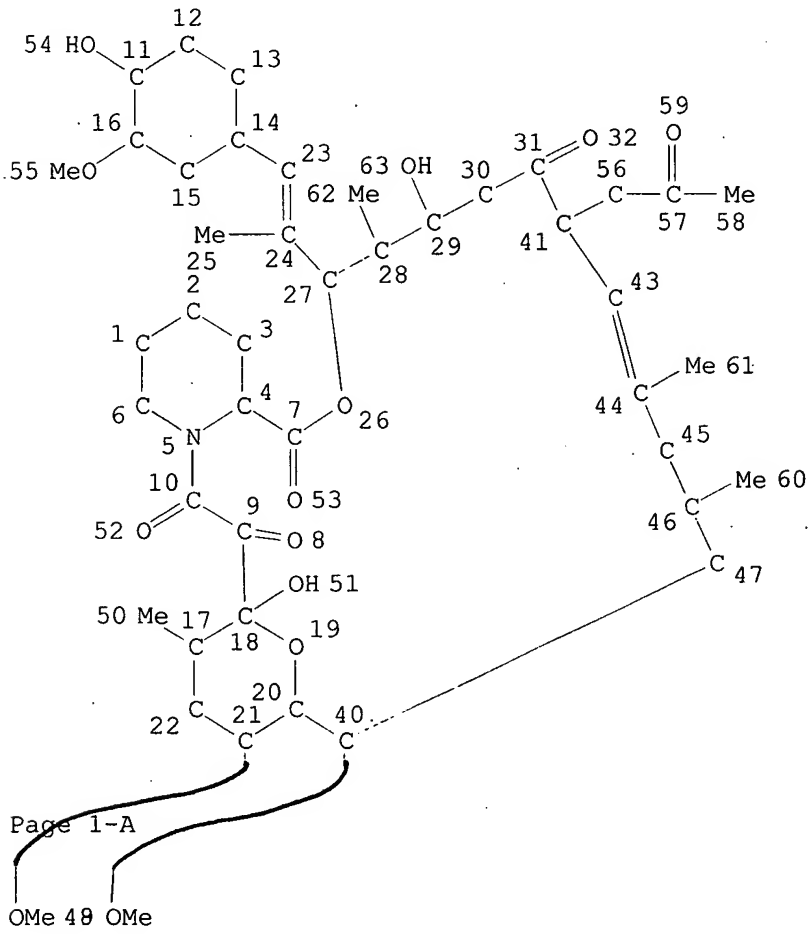

Page 1-A

Page 2-A

NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 55

STEREO ATTRIBUTES: NONE
L9 2 SEA FILE=REGISTRY SSS FUL L7

100.0% PROCESSED 3315 ITERATIONS 2 ANSWERS
SEARCH TIME: 00.00.01

FILE 'CAPLUS' ENTERED AT 15:56:27 ON 15 SEP 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE 'USPATFULL' ENTERED AT 15:56:27 ON 15 SEP 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'TOXCENTER' ENTERED AT 15:56:27 ON 15 SEP 2003
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L21 8 L9

=> dup rem l21
PROCESSING COMPLETED FOR L21
L22 7 DUP REM L21 (1 DUPLICATE REMOVED)
ANSWERS '1-6' FROM FILE CAPLUS
ANSWER '7' FROM FILE USPATFULL

=> d ibib abs hitstr 1-7; fil hom

L22 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2001:63812 CAPLUS
DOCUMENT NUMBER: 134:110473
TITLE: New use of a macrolide tacrolimus analog as a neuroprotectant agent
INVENTOR(S): Jones, Paul Alexander; Sharkey, John; Kelly, John Shearer
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 9 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001005385	A2	20010125	WO 2000-GB2788	20000719
WO 2001005385	A3	20010802		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,

YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
EP 1196170 A2 20020417 EP 2000-946165 20000719
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
JP 2003504396 T2 20030204 JP 2001-510442 20000719
PRIORITY APPLN. INFO.: GB 1999-17158 A 19990721
WO 2000-GB2788 W 20000719

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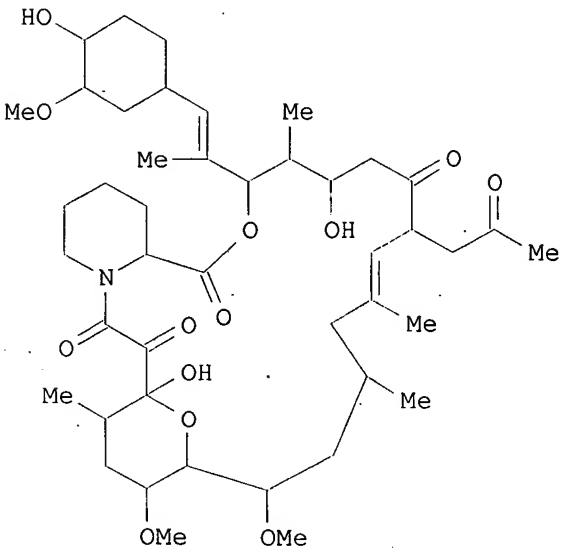


I

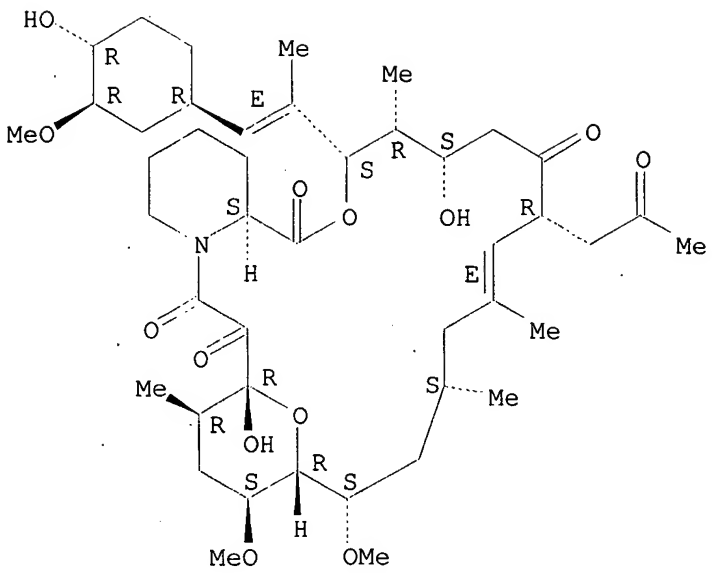
AB A macrolide tacrolimus analog I is provided for use as a neuroprotective agent, particularly for preventing or treating acute or chronic cerebral neurodegenerative diseases.

IT **124554-37-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(macrolide tacrolimus analog as neuroprotectant)

RN 124554-37-6 CAPLUS

CN 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, 5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-oxopropyl)-, (3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L22 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:521493 CAPLUS
DOCUMENT NUMBER: 137:73272
TITLE: Neurotrophic tacrolimus analogs, and therapeutic use
INVENTOR(S): Matsuoka, Nobuya; Yamaji, Takayuki; Gold, Bruce
PATENT ASSIGNEE(S): Japan
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002053159	A1	20020711	WO 2001-US50419	20011231

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-258500P P 20001229

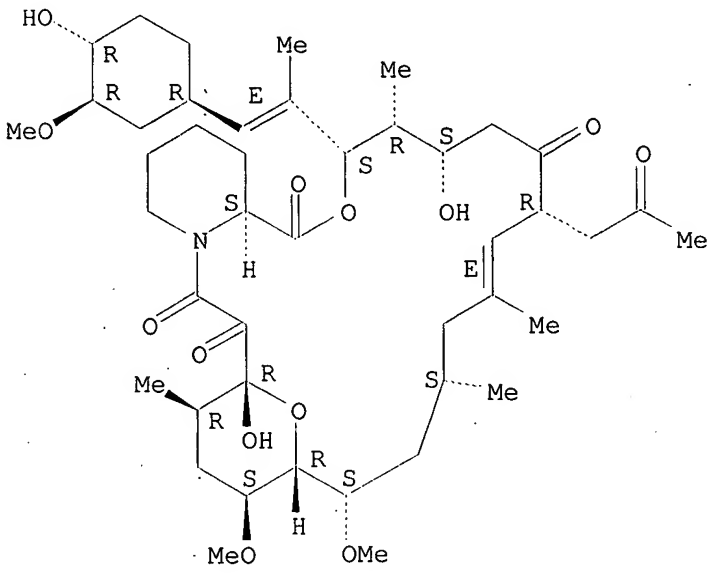
AB The invention discloses tacrolimus derivs. having high levels of neurotrophic activity and low levels of immunosuppressive activity. These compds. are useful as neurotrophic agents, particularly, for preventing or treating neuronal injury/dysfunction.

IT **124554-37-6 150652-88-3 150652-88-3D**, derivs.
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neurotrophic tacrolimus analogs, and therapeutic use)

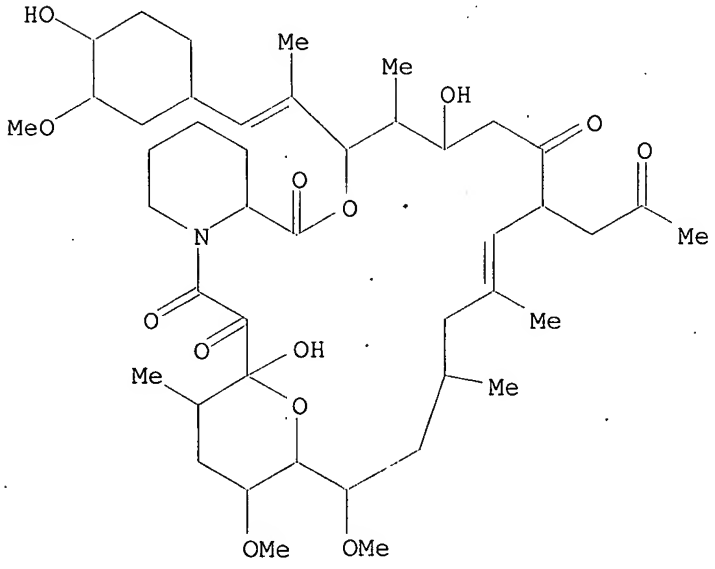
RN 124554-37-6 CAPLUS
CN 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, 5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-

methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-oxopropyl)-, (3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)- (9CI) (CA INDEX NAME)

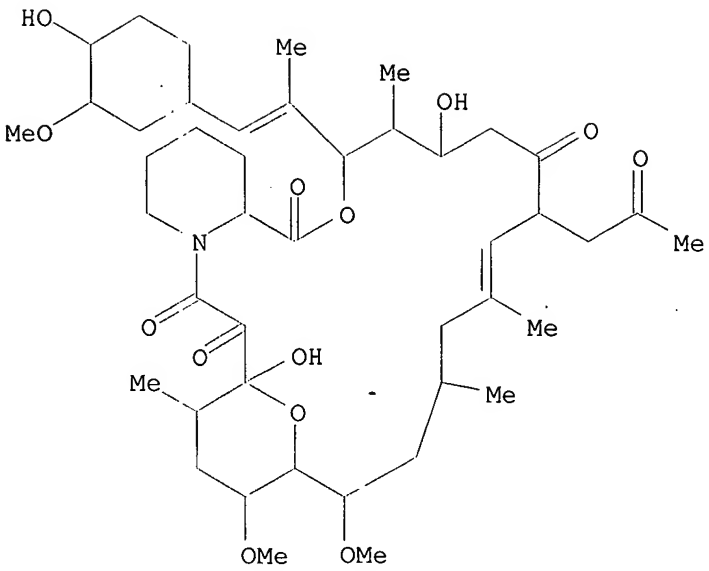
Absolute stereochemistry.
Double bond geometry as shown.



RN 150652-88-3 CAPLUS
CN 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, 5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-oxopropyl)- (9CI) (CA INDEX NAME)



RN 150652-88-3 CAPLUS
CN 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, 5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-oxopropyl)- (9CI) (CA INDEX NAME)

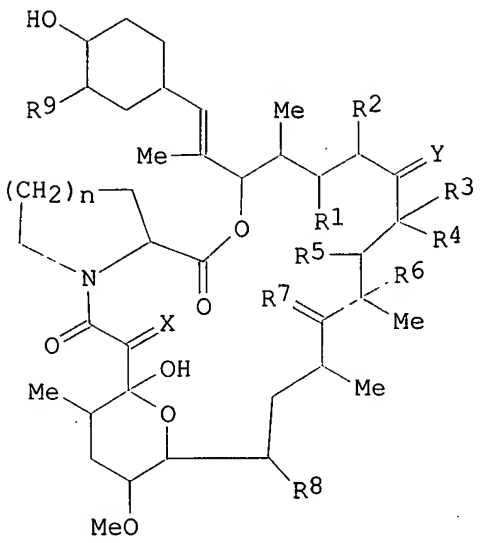


REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1994:280293 CAPLUS
DOCUMENT NUMBER: 120:280293
TITLE: Pharmaceutical compositions and use of macrolide compounds for the treatment of reversible obstructive airways disease
INVENTOR(S): Hallam, Catherine; Harper, Stephen Thomas
PATENT ASSIGNEE(S): Fisons PLC, UK
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9404148	A1	19940303	WO 1993-GB1769	19930820
W: AU, CA, JP, KR, NO, NZ				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
ZA 9306137	A	19940221	ZA 1993-6137	19930820
AU 9349671	A1	19940315	AU 1993-49671	19930820

PRIORITY APPLN. INFO.: GB 1992-18027 A 19920825
WO 1993-GB1769 W 19930820
OTHER SOURCE(S): MARPAT 120:280293
GI



I

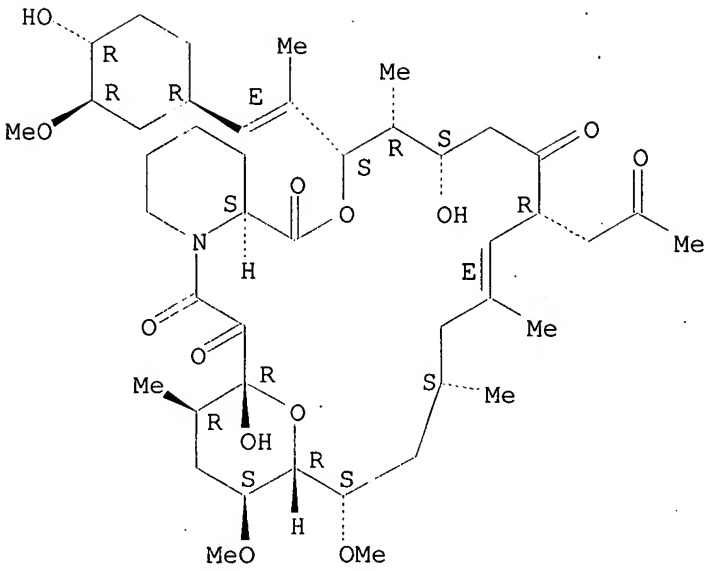
AB The title macrolides I [R1, R2 = H, OH, or may together represent a 2nd C-C bond between the C atoms to which they are attached; R3 = (CO2H-substituted) Me, (O- or OH- or CO2H-substituted) Et, (O- or OH-substituted) Pr, (OH-substituted) allyl; R4 = H; R5 and R6 together represent a 2nd C-C bond between the C atoms to which they are attached; R7 represents O, (H, R7a) (R7a = H, OH); R8, R9 = OH, OCH3; X, Y = O, (H, OH); n = 1,2; in addn. to the above, R1 and R5; R7a and R8; and R3, R4 and Y may form various rings together with the C atoms to which they are attached; with certain provisos], and pharmaceutically acceptable derivs. thereof, are used in the manuf. of a medicament for the treatment of reversible obstructive airways diseases. An aerosol formulation of 17-(2-oxopropyl)-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]octacos-18-ene-2,3,10,16-tetraone (II) is presented. II was tested in a mast cell screen and was found to inhibit histamine release by 50% of its max. value at 1 X 10-8 M.

IT **124554-37-6 124554-37-6D**, derivs.
RL: BIOL (Biological study)
(for reversible obstructive airways disease treatment)

RN 124554-37-6 CAPLUS

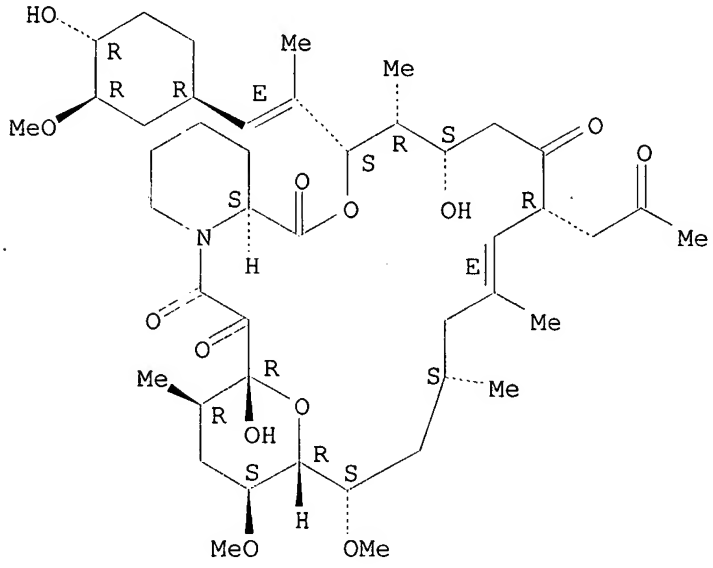
CN 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, 5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-oxopropyl)-, (3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 124554-37-6 CAPLUS
CN 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, 5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-oxopropyl)-, (3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L22 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1993:617378 CAPLUS
DOCUMENT NUMBER: 119:217378
TITLE: Macrocyclic compounds in the prophylactic treatment of AIDS
INVENTOR(S): Orr, Thomas Samuel Campbell
PATENT ASSIGNEE(S): Fisons PLC, UK

Searched by Barb O'Bryen, STIC 308-4291

SOURCE: PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9314771	A1	19930805	WO 1993-GB207	19930201
W: AU, BG, BR, CA, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, UA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG				
AU 9334567	A1	19930901	AU 1993-34567	19930201
ZA 9300691	A	19930906	ZA 1993-691	19930201
PRIORITY APPLN. INFO.:			GB 1992-2196	19920201
			WO 1993-GB207	19930201

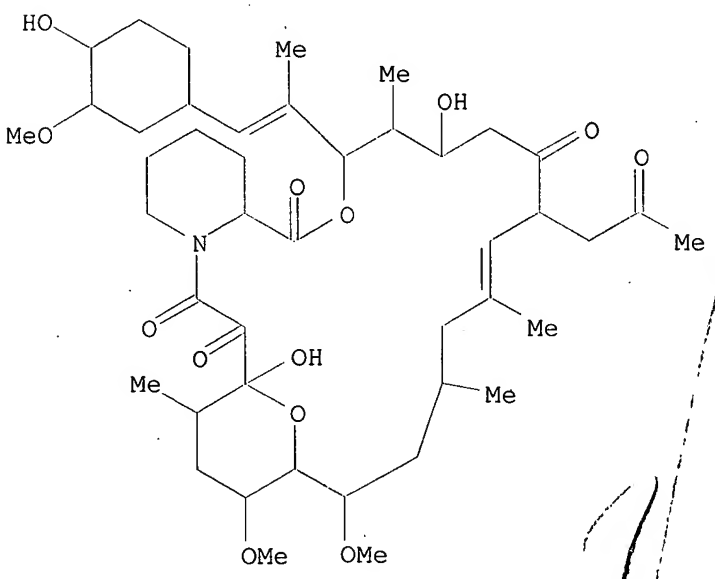
OTHER SOURCE(S): MARPAT 119:217378

AB Derivs. or homologs of 12-(2-cyclohexyl-1-methylvinyl)-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]octacos-18-ene are used in the prophylactic treatment of AIDS.

IT **150652-88-3**
RL: BIOL (Biological study)
(for prophylactic treatment of AIDS)

RN 150652-88-3 CAPLUS

CN 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, 5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-oxopropyl)- (9CI) (CA INDEX NAME)



L22 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1992:6340 CAPLUS
DOCUMENT NUMBER: 116:6340
TITLE: Preparation of rapamycin analogs for treatment of immunosuppression
INVENTOR(S): Donald, David Keith; Furber, Mark; Hardern, David Norman; Leff, Paul
PATENT ASSIGNEE(S): Fisons PLC, UK

Searched by Barb O'Bryen, STIC 308-4291

SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9104025	A1	19910404	WO 1990-GB1412	19900913
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RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE				
CA 2065425	AA	19910315	CA 1990-2065425	19900913
EP 491797	A1	19920701	EP 1990-913838	19900913
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE				
JP 05500215	T2	19930121	JP 1990-512909	19900913

PRIORITY APPLN. INFO.: GB 1989-20849 19890914
GB 1989-20985 19890915
GB 1990-6449 19900322
GB 1990-12795 19900608
GB 1990-14959 19900706
WO 1990-GB1412 19900913

OTHER SOURCE(S): MARPAT 116:6340

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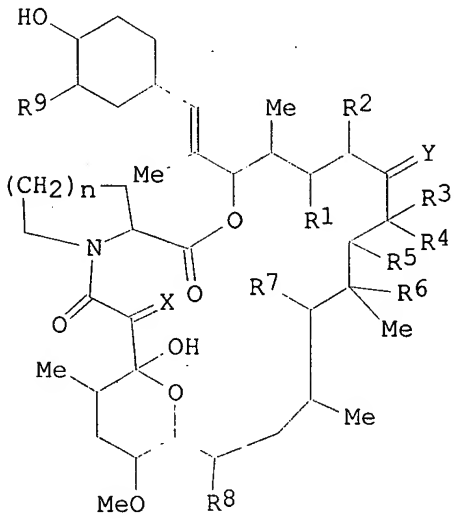


I

AB The title compds. [I; R1,R2,R7 = H, OH; R1R2 = bond; R3 = Me, CH2CH2OH, (un)esterified or (un)amidated (CH2)m CO2H, etc.; R4 = H; R5R6 = bond; R8 = OMe; R9 = OH, OMe; R1R5 = O and R6R7 = bond; R7R8 = O and R3R4Y = atoms to complete a Me-substituted furanyl ring; X, Y = O, (H,OH); m = 1-3; n= 1,2] were prepd. Thus, a DMF soln. of I (R5R6 = bond, R4 = R7 = H, R8 = R9 = OMe, X = Y = O, n = 2) (II; R1R2 = bond, R3 = CH2CH:CH2) contg. PdCl2 and CuCl was oxygenated 3 h and the product hydrogenated over Pd/C to give II (R3 = CH2COMe) (IV; R1 = R2 = H). IV (R1 = OH, R2 = H) had pA2 of 8.3 in the mixed lymphocyte reaction against FR-900506.

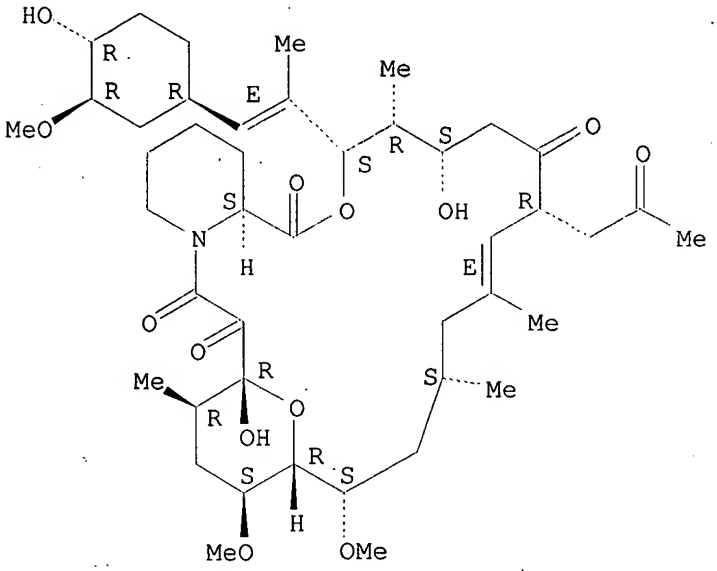
IT **124554-37-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as immunosuppressive antagonist)

RN 124554-37-6 CAPLUS

CN 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, 5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-

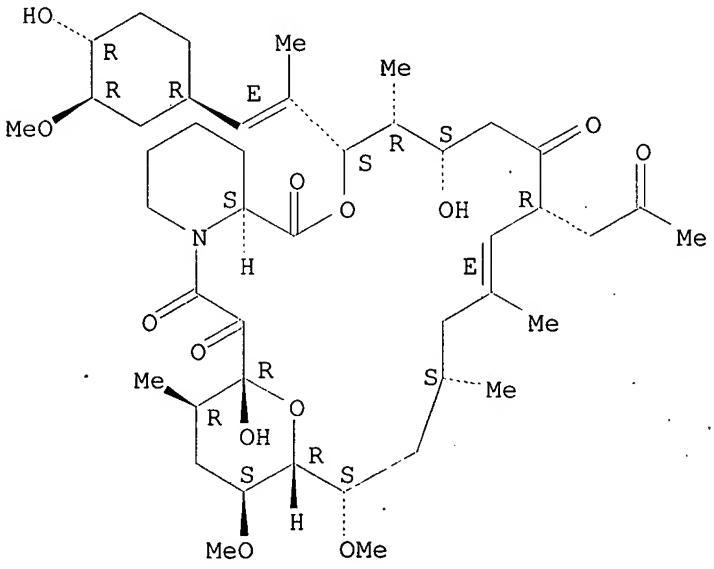
methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-oxopropyl)-, (3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



IT **124554-37-6**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, in prepn. of immunosuppressive antagonists)
RN 124554-37-6 CAPLUS
CN 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, 5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-oxopropyl)-, (3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

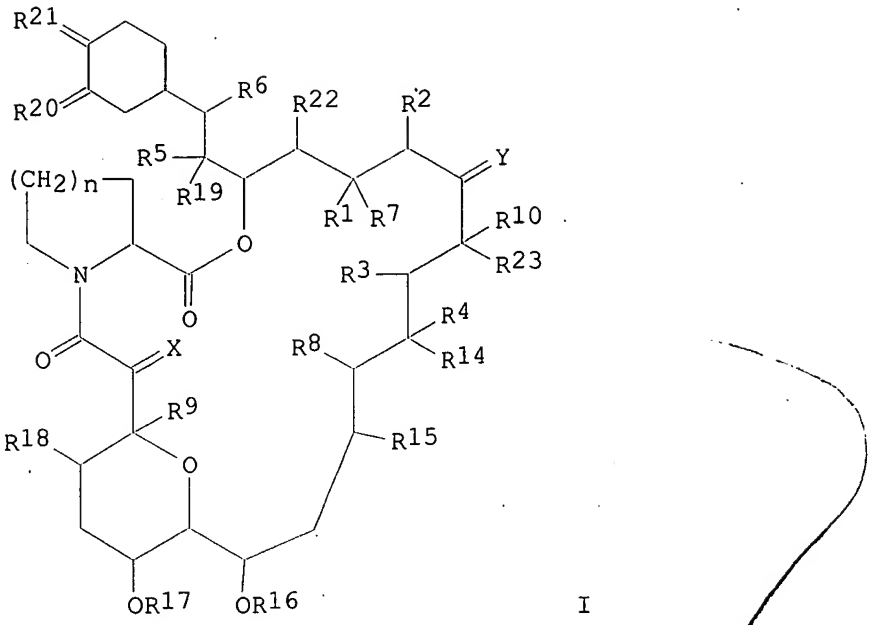


L22 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1990:458793 CAPLUS
DOCUMENT NUMBER: 113:58793
TITLE: Preparation of macrolide compounds as immunosuppressants
INVENTOR(S): Cooper, Martin Edward; Donald, David Keith; Hardern, David Norman
PATENT ASSIGNEE(S): Fisons PLC, UK
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 8905304	A1	19890615	WO 1988-GB1093	19881202
W: AU, DK, FI, HU, JP, KR, NO, US				
RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
AU 8928228	A1	19890705	AU 1989-28228	19881202
AU 630866	B2	19921112		
EP 323042	A1	19890705	EP 1988-311422	19881202
R: ES, GR				
EP 346427	A1	19891220	EP 1989-900628	19881202
EP 346427	B1	19950329		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
JP 02502463	T2	19900809	JP 1989-500404	19881202
AT 120466	E	19950415	AT 1989-900628	19881202
ES 2071681	T3	19950701	ES 1989-900628	19881202
ZA 8809136	A	19890830	ZA 1988-9136	19881206
CA 1339128	A1	19970729	CA 1988-585220	19881207
IL 88629	A1	19940412	IL 1988-88629	19881208
CN 1033458	A	19890621	CN 1988-108277	19881209
US 5376663	A	19941227	US 1989-391538	19890725
NO 8903166	A	19890804	NO 1989-3166	19890804
DK 8903878	A	19890808	DK 1989-3878	19890808
FI 90550	B	19931115	FI 1989-3750	19890809
FI 90550	C	19940225		

PRIORITY APPLN. INFO.:	GB 1987-28820	19871209
	GB 1987-28821	19871209
	GB 1988-3370	19880213
	GB 1988-3371	19880213
	GB 1988-3372	19880213
	GB 1988-3373	19880213
	GB 1988-3374	19880213
	GB 1988-3375	19880213
	GB 1988-3377	19880213
	GB 1988-9174	19880419
	GB 1988-17624	19880723
	GB 1988-18426	19880803
	WO 1988-GB1093	19881202

OTHER SOURCE(S): MARPAT 113:58793
GI



I

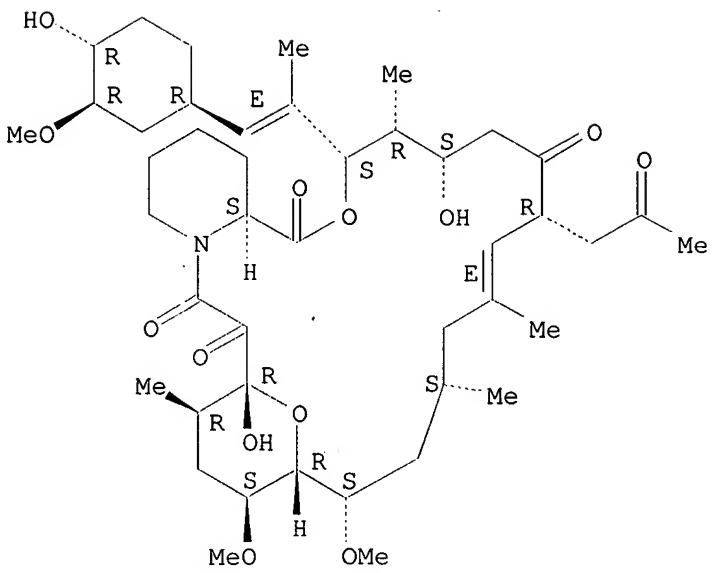
AB The title compds. [I; R1R2, R3R4, R5R6 = 2 vicinal H, bond; or R2 = alkyl; R7 = H, OH, alkoxy; or R7R1 = O; R8,R9 = H, OH; R10 = H, (.gtoreq.1 hydroxy substituted) alkyl or alkenyl, (oxo)alkyl; X = O, (H, OH), (H, H) or CH2O; Y = O, (H, OH), (H, H), NNR11R12, NOR13; R11, R12 = H, alkyl, aryl, tosyl; R13-R19, R22, R23 = H, alkyl; R20, R21 = O, (R24, H), (R25, H); R24, R25 = OH, alkoxy, (OCH2)2CH2OMe; or R24R25 = O in an epoxide ring; n = 1-6; or CY, CR10, or CR23 = 5- or 6-membered N-, S- or O-contg. (un)substituted heterocyclyl; with provisos that, e.g. when X = Y = O, then R9 = R25 = OH, R14-R19 = R22 = Me, R24 = MeO, R8 = R23 = H, R3R4 = R5R6 = bond], useful as immunosuppressants, were prepd. To a stirred soln. of the macrolide FR900506 (200 mg) isolated from Streptomyces (European patent application 0184162) in CH2Cl2 and Et2O was added BF3.Et2O and then a soln. of CH2:N2 (600 mg) in Et2O added slowly over 5 min to give, after purifn. by silica gel chromatog., 55 mg 17-allyl-1-hydroxy-12-[2-(3,4-dimethoxycyclohexyl)-1-methylvinyl-14,23,25-trimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]octacos-19-ene-2,3,10,10-tetraone. This inhibited the proliferation of lymphocytes with an IC50 of <1 .times. 10-6 M.

IT **124554-37-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as immunosuppressant)

RN 124554-37-6 CAPLUS

CN 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, 5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-oxopropyl)-, (3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L22 ANSWER 7 OF 7 USPATFULL on STN

ACCESSION NUMBER:	94:113026 USPATFULL
TITLE:	Macrocyclic compounds
INVENTOR(S):	Cooper, Martin E., Loughborough, England Donald, David K., Ashby de la Zouch, England Hardern, David N., Loughborough, England
PATENT ASSIGNEE(S):	Fisons plc, Ipswich, United Kingdom (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5376663		19941227	
	WO 8905304		19890615	
APPLICATION INFO.:	US 1989-391538		19890725	(7)
	WO 1988-GB1093		19881202	
			19890725	PCT 371 date
			19890725	PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	GB 1987-28820	19871209

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Bond, Robert T.
LEGAL REPRESENTATIVE:	McAulay Fisher Nissen Goldberg & Kiel
NUMBER OF CLAIMS:	8
EXEMPLARY CLAIM:	1,8
LINE COUNT:	1094

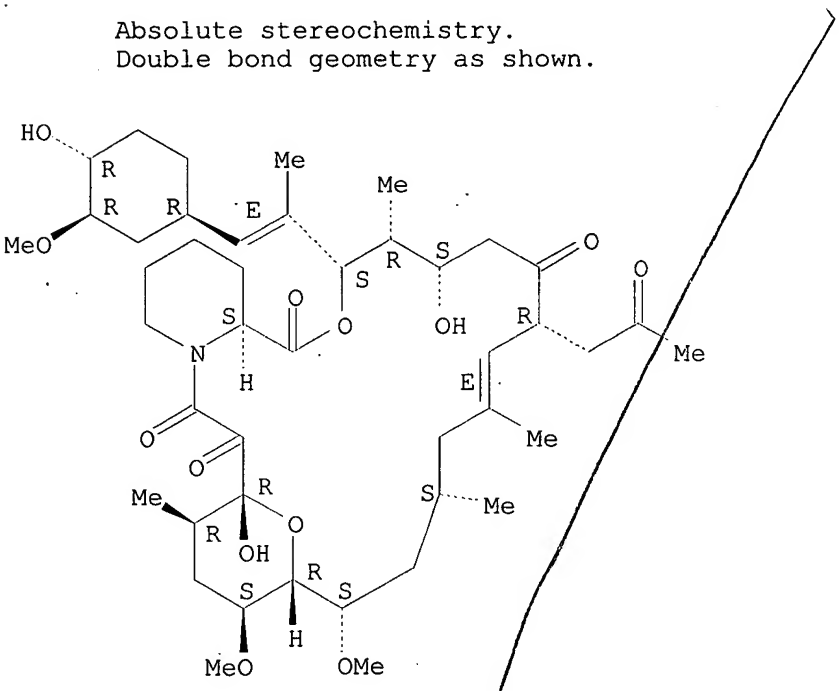
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds of formula (I), in which [R.sup.1 and R.sup.2], [R.sup.3 and R.sup.4] and [R.sup.5 and R.sup.6] represent a carbon-carbon bond or two hydrogen atoms; R.sup.2 additionally represents alkyl; R.sup.7, R.sup.8 and R.sup.9 represent groups including H or OH, R.sup.10 has various significances including alkyl and alkenyl; X and Y represent groups including O and (H, OH); R.sup.14, R.sup.15, R.sup.16, R.sup.17, R.sup.18, R.sup.19, R.sup.22 and R.sup.23 represent H or alkyl; R.sup.20 and R.sup.21 represent groups including O, (H, OH) and (H, O-alkyl), n is 1, 2 or 3, and in addition, Y, R.sup.10 and R.sup.23, together with the carbon atoms to which they are attached, may represent a

heterocyclic ring, (with certain provisos) are described. Processes for making the compounds and pharmaceutical formulations containing them, e.g. for use as immunosuppressive agents, are also described. ##STR1##

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **124554-37-6P**
(prepn. of, as immunosuppressant)
RN 124554-37-6 USPATFULL
CN 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, 5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-oxopropyl)-, (3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



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